(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27096 A1

(51) International Patent Classification[7]: C07D 277/64, 417/12, 417/14, 213/75, 241/08, 277/24, 277/28, 417/04, C07C 233/87, 311/18, 311/41, C07K 5/062, A61K 31/425, 31/18, 31/165, 31/44, 31/495, 38/05, A61P 11/06, 29/00

(21) International Application Number: PCT/GB00/03832

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9923710.9 8 October 1999 (08.10.1999) GB

(71) Applicant *(for all designated States except US)*: **PROTHERICS MOLECULAR DESIGN LIMITED** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LIVELY, Sarah, Elizabeth** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB). **WASZKOWYCZ, Bohdan** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB). **HARRISON, Martin, James** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB). **CLASE, Juha, Andrew** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB). **NAYLOR, Neil, Jason** [GB/GB]; Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL (GB).

(74) Agent: **HAY, Martin, Alexander**; Martin A. Hay & Co., 13 Queen Victoria Street, Macclesfield, Cheshire SK11 6LP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

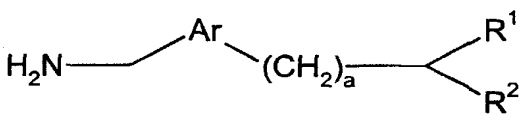
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/27096 A1

(54) Title: AMINOMETHYL-(HETERO)ARYL DERIVATIVES AND THEIR USE AS TRYPTASE INHIBITORS



(I)

(57) Abstract: Compounds of general formula (I) in which Ar, a, R^1 and R^2 and have any of the meanings given in the specification, are tryptase inhibitors useful in the treatment of inflammatory and other conditions, such as asthma.

AMINOMETHYL –(HETERO)ARYL DERIVATIVES AND THEIR USE AS TRYPTASE INHIBITORS

The present invention relates to chemical compounds useful as pharmaceuticals. More particularly it relates to certain novel aminomethyl derivatives, to pharmaceutical compositions comprising aminomethyl derivatives, to the use of aminomethyl derivatives as tryptase inhibitors, to a process for preparing aminomethyl derivatives, and to intermediates useful in the preparation of aminomethyl derivatives.

Tryptase is an enzyme that belongs to a large class of enzymes known as the serine proteases. It is secreted by mast cells and has been found to be involved in a variety of biological processes, such as inflammation. It is believed to be a mediator in the development of such diseases as asthma, allergic rhinitis, inflammatory bowel disease, eczema, psoriasis, atopic dermatitis, urticaria, conjunctivitis and rheumatoid arthritis. Inhibitors of the enzyme are therefore envisaged to be useful in the treatment of mast cell mediated diseases such as these (See, for example, Kyle C Elrod & Robert P Numerof, "Emerging therapeutic targets in asthma: the rationale for mast cell tryptase inhibition", Emerging Therapeutic Targets (1999) 3(2), 203-212).

A variety of tryptase inhibitors are known in the art.

International patent application publication number WO 9926925 discloses certain pyrimidinones having tryptase inhibitor activity. The exemplified compounds all possess a strongly basic amidine or guanidine group.

International patent application publication number WO 9532945 discloses certain bis-aminomethyl and guanidyl derivatives having tryptase inhibitor activity. The exemplified compounds include certain bis-aminomethylphenyl

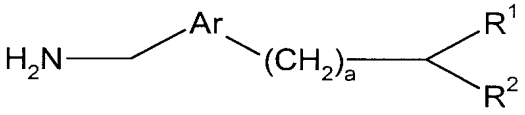
derivatives (i.e. compounds having an aminomethylphenyl group at each end of the molecule).

International patent application publication number WO 9940073 discloses certain bifunctional compounds as tryptase inhibitors. The exemplified compounds include certain bis-aminomethylphenyl derivatives (i.e. compounds having an aminomethylphenyl group at each end of the molecule).

International Patent Application Publication Number WO 9720822 discloses N-[4-(aminomethyl)benzyl]naphthalene-1-sulfonamide as an intermediate.

Novel compounds possessing one aminomethyl group have now been found which are tryptase inhibitors.

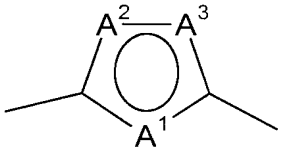
According to one aspect, therefore, the present invention provides a compound of general formula I



I

in which:-

Ar represents an aromatic ring of formula



which is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group;

A^1 represents O, NH, S, CH or CH=CH; and A^2 and A^3 are each selected independently from CH, O, S, N and NH; provided that

A^1, A^2 and A^3 are selected so that they, together with the carbon atoms to which they are attached, form an aromatic ring;

R^1 represents a hydrogen atom, an amino group or a group of formula $NHX^1(CH_2)_bR^3$;

R^2 represents a group of formula COR^4 or, when R^1 represents a group of formula $NHX^1(CH_2)_bR^3$, a hydrogen atom;

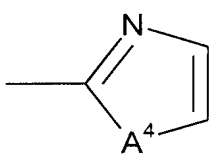
X^1 represents a bond, CO, SO_2, COO or CONH;

a represents 0, 1 or 2;

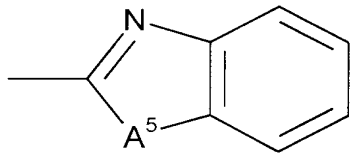
b represents 0 or an integer of from 1 to 4;

R^3 represents an unsubstituted or substituted aromatic, heterocyclic, (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl or (3-10C)cycloalkyl group;

R^4 represents a group of formula COR^5, a group of formula CF_2R^6 or an unsubstituted or substituted heteroaromatic group of formula



or



R^5 represents a (1-6C)alkyl, fluoro(1-6C)alkyl or (3-10C)cycloalkyl group, an unsubstituted or substituted aromatic or heterocyclic group, a group of formula OR^7 or a group of formula NR^8R^9;

R^6 represents a fluorine atom, a (1-6C)alkyl, fluoro(1-6C)alkyl or (3-10C)cycloalkyl group, an unsubstituted or substituted aromatic or heterocyclic group, a group of formula $COOR^{10}$ or a group of formula $CONR^{11}R^{12}$;

A^4 represents O, NH or S;

A^5 represents O, NH or S; and

R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each selected independently from a hydrogen atom, a (1-6C)alkyl group, a (3-6C)cycloalkyl group and an unsubstituted or substituted aromatic group; or respectively R^8 and R^9 or R^{11} and R^{12} together with the nitrogen atom to which they are attached
form a 5-6 membered heterocyclic ring; but excluding N-[4-(aminomethyl)benzyl]naphthalene-1-sulfonamide;
or a pharmaceutically acceptable metabolically labile amide thereof; or a pharmaceutically acceptable salt of said compound of formula I or said metabolically labile amide thereof.

Compounds of formula I have been found to possess activity as tryptase inhibitors.

As used herein, the term unsubstituted or substituted in relation to a group and without further qualification signifies that the group is unsubstituted or substituted by one or more (for example one, two or three) substituents, said substituent or substituents being selected from any atom and group (other than a group containing an aminomethylphenyl group) which, when present in the compound of formula I, do not prevent the compound of formula I from functioning as a tryptase inhibitor.

The term aromatic group as used herein includes a phenyl or naphthyl group, such as 1-naphthyl or 2-naphthyl.

The term heterocyclic group includes a heteroaromatic group and a non-aromatic heterocyclic group.

The term heteroaromatic group includes a 5- or 6-membered aromatic ring containing from one to four heteroatoms selected from O, N and S, the remaining ring atoms being carbon, which ring may be fused with a benzene ring or a second 5- or 6-membered aromatic ring containing from one to four heteroatoms selected from O, N and S, the remaining ring atoms being carbon. Examples of a heteroaromatic group are furyl, benzofuryl, thienyl, benzothienyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, imidazolyl, benzimidazolyl, pyrrolyl, indolyl, pyridyl and pyrimidyl.

An unsubstituted or substituted aromatic or heteroaromatic group may, for example, be unsubstituted or substituted by (1-4C)alkylenenedioxy or by one, two or three substituents selected independently from

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a (3-7C)cycloalkyl(1-4C)alkyl group;

a halo(1-4C)alkyl group;

a group of formula $(CH_2)_cX^2(CH_2)_dX^3R^{13}$ in which c represents 0, 1 or 2, d represents 0, 1 or 2, X^2 represents O, S, SO, SO_2, NR^{14}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, X^3 represents a bond, O, S, SO, SO_2, NR^{15}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{13} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula $(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents

0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$ or SO_2NH and R^{38} represents a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group, R^{14} and R^{15} each independently represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{13} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenenedioxy, or one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_eX^4(CH_2)_fR^{16}$ in which e represents 0, 1 or 2, f represents 0, 1 or 2, X^4 represents O, S, SO, SO_2, NR^{17}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{16} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{17} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{16} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

An aromatic or heteroaromatic group represented by R^{13} may be, for example, a thienyl, pyridyl, naphthyl or phenyl group.

R^{13} may represent, for example, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group.

Examples of particular values are:

for X^2: O, SO_2, NH, $NHCH_3$, CONH, NHCO, NHCOO or SO_2NH;

for X^3: a bond or O;

for c: 0;

for d: 0, 1 or 2; and

for R^{13}: methyl, isopropyl, cyclohexyl, indan-1-yl, pyrid-4-yl, naphth-1-yl, naphth-2-yl, phenyl, 2-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methylphenyl, 4-methylphenyl or 4-isopropylphenyl.

for X^{14}: 0;

for w: 0 or 1

for x: 0 or 1

for R^{38}: methyl or phenyl.

Examples of particular values for a substituent on a substituted aromatic group or a substituted heteroaromatic group are methylenedioxy, nitro, methyl, isopropyl, cyclohexylmethyl, amino, methoxy, isopropoxy, phenoxy, benzyloxy, phenoxyethoxy, dimethylamino, acetylamino, phenylacetylamino, cyclohexylamido, cyclohexylmethylaminocarbonyl, indan-1-ylaminocarbonyl, pyrid-4-ylaminocarbonyl, naphth-1-ylamido, naphth-2-ylamido, benzamido, benzoylamino, 3-methylbenzylaminocarbonyl, 4-methylbenzylaminocarbonyl, 2-fluorobenzylaminocarbonyl, 3-chlorobenzylamido, 4-chlorobenzylamido, benzylamido, benzylsulfonylamino, 4-isopropylbenzamido, benzyloxycarbonylamino, methanesulfonyl, hydroxy and phenyl.

Examples of particular values for an unsubstituted or substituted aromatic group are phenyl, 2-naphthyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-isopropylphenyl, 3-methyl-4-nitrophenyl, 3-methyl-4-aminophenyl, 4-isopropoxyphenyl, 3,4-dimethoxyphenyl, 4-phenylphenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, 4-(2-phenoxyethoxy)phenyl, 4-(N,N-dimethylamino)phenyl, 4-(N-acetylamino)phenyl, 4-methanesulphonylphenyl and 4-hydroxyphenyl.

Examples of particular values for an unsubstituted or substituted heteroaromatic group are thien-2-yl, pyrrol-2-yl, 3-benzyloxycarbonylamino-6-methyl-pyrid-2-one-1-yl, 3-acetylamino-6-methyl-pyrid-2-one-1-yl and 3-benzyloxycarbonylamino-6-cyclohexylmethyl-pyrid-2-one-1-yl, thiazol-2-yl, benzothiazol-2-yl, 6-benzylaminocarbonylbenzothiazol-2-yl, 5-phenyl-thiazol-2-yl, 6-phenylcarboxamidobenzothiazol-2-yl, 6-(4-methyl)benzylaminocarbonylbenzothiazol-2-yl, 6-cyclohexylmethylaminocarbonylbenzothiazol-2-yl, 6-phenylaminocarbonylbenzothiazol-2-yl, 6-(3-methylbenzylaminocarbonylbenzothiazol-2-yl, 6-indan-1-ylaminocarbonyl-benzothiazol-2-yl, 6-(2-fluoro)benzylaminocarbonylbenzothiazol-2-yl, 6-(4-chloro)benzylcarbonylaminobenzothiazol-2-yl, 6-(3-chloro)benzylcarbonylaminobenzothiazol-2-yl, 6-cyclohexylcarbonylaminobenzothiazol-2-yl, 6-(4-isopropyl)phenylcarbonylaminobenzothiazol-2-yl, 6-naphth-1-ylcarbonylaminobenzothiazol-2-yl, 6-naphth-2-ylcarbonylaminobenzothiazol-2-yl, 6-benzylsulfonylaminobenzothiazol-2-yl, and 6-pyrid-4-ylaminocarbonylbenzothiazol-2-yl.

The term non-aromatic heterocyclic group includes a non-aromatic 5- or 6-membered ring containing from one to four heteroatoms selected from O, N and S, the remaining ring atoms being carbon, which ring may be fused with a non-aromatic or aromatic carbocyclic ring or a second 5- or 6-membered aromatic or non-aromatic ring containing from one to four heteroatoms selected from O, N and S, the remaining ring atoms being carbon. Examples of a non-aromatic heterocyclic group are pyrrolidinyl, such as pyrrolidin-2-yl, piperidinyl, such as piperidin-4-yl, piperazinyl, such as piperazin-3-yl and 2,3-dihydrobenzofuranyl, such as 2,3-dihydrobenzofuran-5-yl.

An unsubstituted or substituted non-aromatic heterocyclic group may, for example, be unsubstituted or substituted by one, two or three of:

a (1-4C)alkyl group;

oxo;

a group of formula $-X^6-(CHR^{18})_g-X^7-(CH_2)_h-R^{19}$ in which g represents 0, 1 or 2, h represents 0, 1 or 2, X^6 represents O, S, SO, SO_2, NR^{20}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, X^7 represents a bond, O, S, SO, SO_2, NR^{21}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{18} and R^{19} each independently represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group, a pyrrolyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group, a hydroxy group and a (1-4C)alkoxy group, and R^{20} and R^{21} each independently represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{19} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

a group R^{22} in which R^{22} is (3-7C)cycloalkyl(1-4C)alkyl or a phenyl, naphthyl, phenyl(1-4C)alkyl or naphthyl(1-4C)alkyl group that is unsubstituted or substituted on any phenyl or naphthyl moeity by (1-4C)alkylenedioxy or one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_iX^8(CH_2)_jR^{23}$ in which i represents 0, 1 or 2, j represents 0, 1 or 2, X^8 represents O, S, SO, SO_2, NR^{24}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{23} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is

unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{24} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{23} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

Examples of particular values are:

for X^6: CO;

for R^{18}: hydrogen or methyl;

for X^7: a bond, NHCO or $NHSO_2$;

for R^{19}: methyl, cyclopentyl, cyclohexyl, thien-2-yl, pyrrol-2-yl, phenyl or 4-hydroxyphenyl;

for g: 0 or 1;

for h: 0 or 1; and

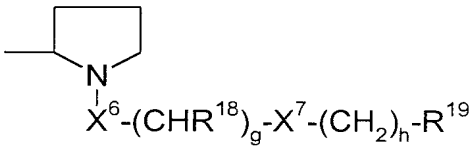
for R^{22}: 2-naphthylmethyl and 3-chlorobenzyl.

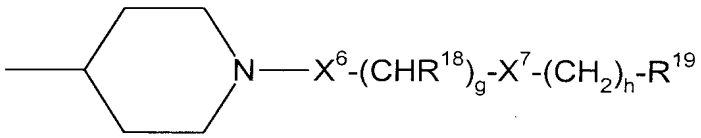
Examples of particular values for a substituent on a substituted non-aromatic heterocyclic group are oxo, acetyl, 2-acetylaminopropionyl, 2-(2-thienyl)acetylaminopropionyl, 2-cyclopentanoylaminopropionyl, pyrrol-2-ylcarbonyl, 2-cyclohexylacetylaminopropionyl, 2-(2-thienyl)carbonylaminopropionyl, 2-(4-hydroxyphenyl)acetylaminopropionyl, 2-phenylsulfonylamino-propionyl, 2-benzylsulfonylaminopropionyl, 2-naphthylmethyl and 3-chlorobenzyl.

Examples of particular values for an unsubstituted or substituted non-aromatic heterocyclic group are 2,3-dihydrobenzofuran-5-yl, 1-acetylpiperidin-4-yl, 1-(2-acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-(2-thienyl)-acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-cyclopentanoylaminopropionyl)pyrrolidin-2-yl, 1-(pyrrol-2-oyl)-pyrrolidin-2-yl, 1-(2-cyclohexylacetylamino-propionyl)pyrrolidin-2-yl, 1-(2-(2-thienyl)carbonylaminopropionyl)pyrrolidin-2-yl, 1-(2-(4-

hydroxyphenyl)acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-phenylsulfonylaminopropionyl)pyrrolidin-2-yl, 1-(2-benzylsulfonylaminopropionyl)pyrrolidin-2-yl, 6-(naphth-2-yl)methyl-2,5-dioxopiperazin-3-yl and 6-(3-chlorobenzyl)-2,5-dioxopiperazin-3-yl.

An unsubstituted or substituted non-aromatic heterocyclic group may be, for example, a group of formula





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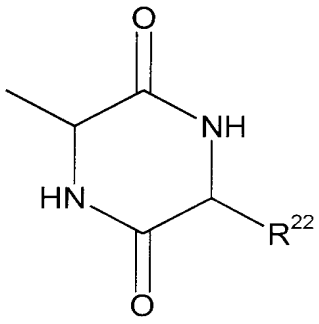


in which X^6, X^7, R^{18}, R^{19}, R^{22}, g and h are as defined above.

The term (1-10C)alkyl signifies a straight chain or branched group. It includes (1-4C)alkyl. Examples of a (1-10C)alkyl group include methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

An unsubstituted or substituted (1-10C) alkyl group may be substituted by, for example, one or two substituents selected from a halogen atom and a (1-4C)alkoxy group. An example of a substituent on a substituted (1-10C)alkyl group is fluoro.

The term (2-10C)alkenyl signifies a straight chain or branched group. It includes (2-4C)alkenyl. Examples of a (2-10C)alkenyl group include ethenyl.

An unsubstituted or substituted (2-10C) alkenyl group may be substituted by, for example, a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group. An example of a substituent on a substituted (2-10C)alkenyl group is phenyl.

The term (2-10C)alkynyl signifies a straight chain or branched group. It includes (2-4C)alkynyl. Examples of a (2-10C)alkynyl group include ethynyl.

An unsubstituted or substituted (2-10C) alkynyl group may be substituted by, for example, a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group. An example of a substituent on a substituted (2-10C)alkynyl group is phenyl.

The term (3-10C)cycloalkyl signifies a saturated monocyclic or polycyclic carbocyclic group. It includes (3-6C)cycloalkyl. Examples of values for a (3-10C)cycloalkyl group include cyclopropyl, cyclobutyl, cyclohexyl and adamantyl.

An unsubstituted or substituted (3-10C)cycloalkyl group may be substituted by, for example, one, two or three (1-4C)alkyl groups. An example of a substituent is methyl.

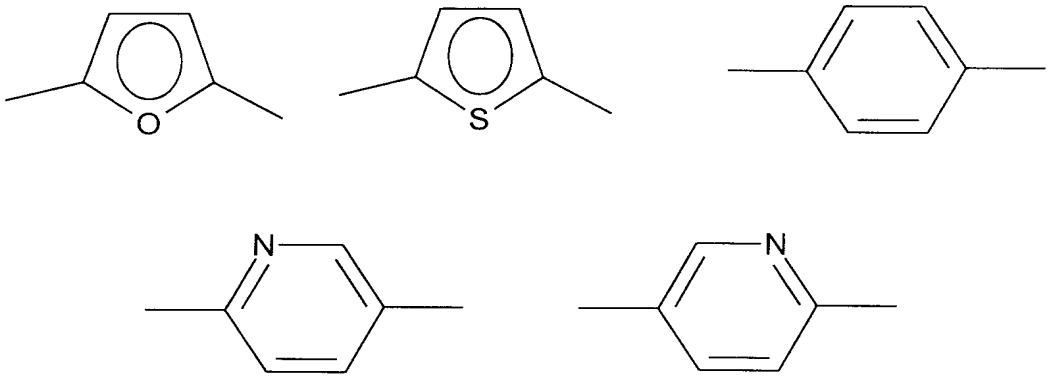
The term (1-4C)alkylenedioxy includes methylenedioxy and ethylenedioxy.

In the compounds of formula I, the group Ar is preferably unsubstituted.

Preferably A^1 represents O, S or CH=CH.

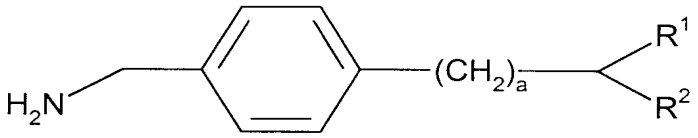
Preferably one of A^2 and A^3 represents CH or N and the other represents CH.

Examples of values for Ar are



Preferably A^1 represents CH=CH and A^2 and A^3 each represents CH.

Accordingly, a preferred group of compounds of formula I is that of formula Ia

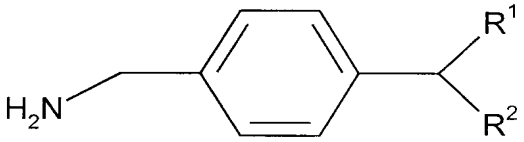


Ia

in which a, R^1 and R^2 are as defined above, or a pharmaceutically acceptable metabolically labile amide thereof or a pharmaceutically acceptable salt of said compound of formula Ia or said metabolically labile amide thereof.

a is preferably 0.

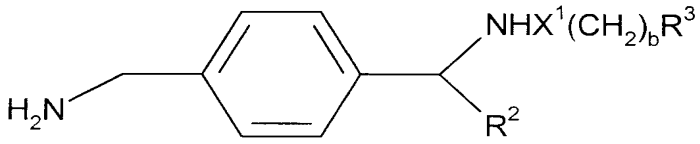
Accordingly, a preferred group of compounds of formula I is that of formula



Ib

R^1 preferably represents a group of formula $NHX^1(CH_2)_bR^3$.

Accordingly, a preferred group of compounds of formula I is that of formula



Ib

X^1 is preferably selected from CO, SO_2 or COO.

b is preferably 0 or 1.

Examples of particular values for R^3 when it represents an unsubstituted or substituted (1-10C) alkyl group are (1-4C)alkyl groups such as methyl, ethyl, propyl and t-butyl.

Examples of particular values for R^3 when it represents an unsubstituted or substituted (2-10C) alkenyl group are (2-4C)alkenyl such as ethenyl, and styryl.

Examples of particular values for R^3 when it represents an unsubstituted or substituted (2-10C)alkynyl group are (2-4C)alkynyl such as ethynyl.

Examples of particular values for R^3 when it represents an unsubstituted or substituted (3-10C)cycloalkyl group are cyclohexyl and adamantyl.

The aromatic group in an unsubstituted or substituted aromatic group represented by R^3 may be, for example, a phenyl, 1-naphthyl or 2-naphthyl group.

The heterocyclic group in an unsubstituted or substituted heterocylic group represented by R^3 may be, for example a heteroaromatic group selected from furyl, benzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyridyl and pyrimidyl.

An unsubstituted or substituted aromatic or heteroaromatic group represented by R^3 may, for example, be unsubstituted or substituted by (1-4C)alkylenenedioxy or by one, two or three substituents selected independently from

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a (3-7C)cycloalkyl(1-4C)alkyl group;

a halo(1-4C)alkyl group;

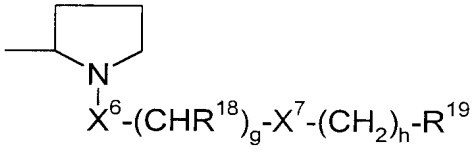
a group of formula $(CH_2)_cX^2(CH_2)_dX^3R^{13}$ in which c represents 0, 1 or 2, d represents 0, 1 or 2, X^2 represents O, S, SO, SO_2, NR^{14}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, X^3 represents O, S, SO, SO_2, NR^{15}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{13} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{14} and R^{15} each independently represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{13} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

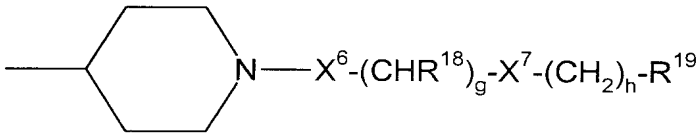
a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenenedioxy, or one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_eX^4(CH_2)_fR^{16}$ in which e represents 0, 1 or 2, f represents 0, 1 or 2, X^4 represents O, S, SO, SO_2, NR^{17}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{16} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{17} represents a hydrogen atom, a (1-4C)alkyl group or, together

with R^{16} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

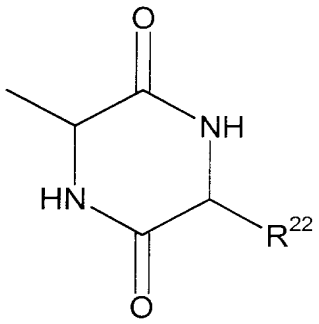
Examples of particular values for R^3 when it represents an unsubstituted or substituted aromatic group are phenyl, 2-naphthyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-isopropylphenyl, 3-methyl-4-nitrophenyl, 3-methyl-4-aminophenyl, 4-isopropoxyphenyl, 3,4-dimethoxyphenyl, 4-phenylphenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, 4-(2-phenoxyethoxy)phenyl, 4-(N,N-dimethylamino)phenyl, 4-(N-acetylamino)phenyl, 4-methanesulphonylphenyl and 4-hydroxyphenyl.

When R^3 represents an unsubstituted or substituted non-aromatic heterocyclic group, this may be, for example, a group of formula





or



Examples of particular values for R^3 when it represents an unsubstituted or substituted heterocyclic group are 2,3-dihydrobenzofuran-5-yl, 1-acetylpiperidin-4-yl, 1-(2-

acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-(2-thienyl)-acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-cyclopentanoylaminopyrrolidin-2-yl, 1-(pyrrol-2-oyl)pyrrolidin-2-yl, 3-benzyloxycarbonylamino-6-methyl-pyrid-2-one-1-yl, 1-(2-cyclohexylacetylaminopropionyl)-pyrrolidin-2-yl, 1-(2-(2-thienyl)carbonylaminopropionyl)-pyrrolidin-2-yl, 1-(2-(4-hydroxyphenyl)acetylaminopropionyl)-pyrrolidin-2-yl, 1-(2-phenylsulfonylaminopropionyl)pyrrolidin-2-yl, 1-(2-benzylsulfonylaminopropionyl)pyrrolidin-2-yl, 3-acetylamino-6-methyl-pyrid-2-one-1-yl, 3-benzyloxycarbonyl-amino-6-cyclohexylmethyl-pyrid-2-one-1-yl, 6-(naphth-2-yl)methyl-2,5-dioxopiperazin-3-yl and 6-(3-chlorobenzyl)-2,5-dioxopiperazin-3-yl.

R^2 preferably represents COR^4.

The heteroaromatic group represented by R^4 may, for example, be unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected independently from

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a halo(1-4C)alkyl group;

a group of formula $(CH_2)_kX^9(CH_2)_mR^{25}$ in which k represents 0, 1 or 2, m represents 0, 1 or 2, X^9 represents O, S, SO, SO_2, NR^{26}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{25} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula

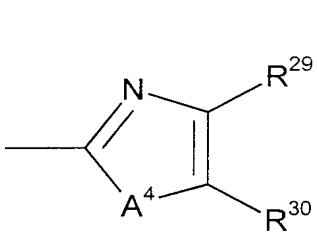
$(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents 0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$, or SO_2NH and R^{38} represent a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a(1-4C)alkyl group, R^{26} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{25} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_nX^{10}(CH_2)_pR^{27}$ in which n represents 0, 1 or 2, p represents 0, 1 or 2, X^{10} represents O, S, SO, SO_2, NR^{28}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{27} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{28} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{27} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

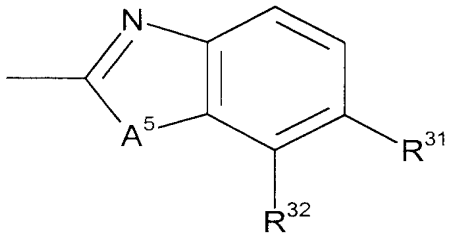
An aromatic or heteroaromatic group represented by R^{25} may be, for example, a thienyl, pyridyl, naphthyl or phenyl group.

R^{25} may represent, for example, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group.

When R^4 represents a heteroaromatic group, this group may, for example, be selected from groups of formula



and



in which:

A^4 and A^5 are as defined above;

R^{29} and R^{30} are together (1-4C)alkylenedioxy or are each selected independently from

a hydrogen atom;

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a halo(1-4C)alkyl group;

a group of formula $(CH_2)_qX^{11}(CH_2)_rR^{33}$ in which q represents 0, 1 or 2, r represents 0, 1 or 2, X^{11} represents O, S, SO, SO_2, NR^{34}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{33} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{34} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{33} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected

from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_sX^{12}(CH_2)_tR^{35}$ in which s represents 0, 1 or 2, t represents 0, 1 or 2, X^{12} represents O, S, SO, SO_2, NR^{36}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{35} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{36} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{35} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

R^{31} and R^{32} are together (1-4C)alkylenedioxy or are each selected independently from

a hydrogen atom;

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a halo(1-4C)alkyl group; and

a group of formula $(CH_2)_uX^{13}(CH_2)_vR^{37}$ in which u represents 0, 1 or 2, v represents 0, 1 or 2, X^{13} represents O, S, SO, SO_2, NR^{38}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{37} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula

$(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents 0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$, or SO_2NH and R^{38} represent a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a(1-4C)alkyl group, R^{38} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{37} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

An examples of a particular value for p is 0.

Examples of particular values for r are 0 or 1.

Examples of particular values for X^{11} are CONH and NHCO.

Examples of particular values for R^{33} are methyl, phenyl and cyclohexyl.

An example of a particular value for R^{34} is hydrogen.

An example of a particular value for s is 1.

An example of a particular value for t is 1.

An example of a particular value for X^{12} is NHCO.

An example of a particular value for R^{35} is phenyl.

An example of a particular value for R^{36} is hydrogen.

An aromatic or heteroaromatic group represented by R^{37} may be, for example, a thienyl, pyridyl, naphthyl or phenyl group.

R^{37} may represent, for example, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group a (1-4C)alkoxy group.

Examples of particular values for R^{37} are cyclohexyl, indan-1-yl, pyrid-4-yl, naphth-1-yl, naphth-2-yl, 2-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methylphenyl, 4-methylphenyl and 4-isopropylphenyl.

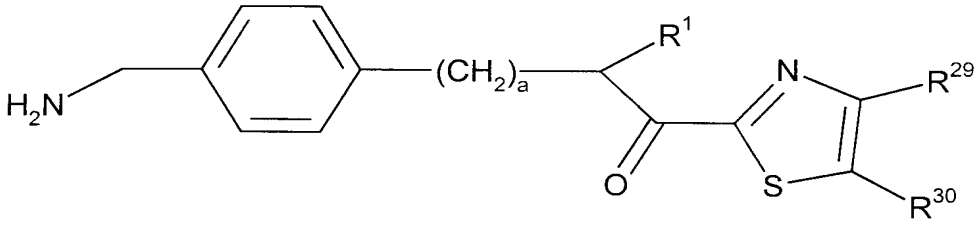
A^4 and A^5 each preferably represents S.

Examples of particular values for R^4 are methoxycarbonyl, thiazol-2-yl, benzothiazol-2-yl, 6-benzylaminocarbonylbenzothiazolyl, 5-phenylthiazol-2-yl, 6-

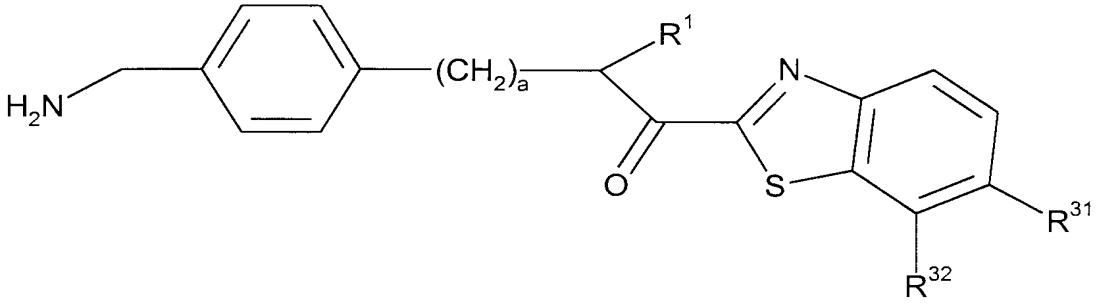
phenylcarboxamidobenzothiazol-2-yl, 6-benzylaminocarbonyl-benzothiazol-2-yl, 6-(4-methyl)benzylaminocarbonylbenzothiazol-2-yl, 6-cyclohexylmethylamino-carbonylbenzothiazol-2-yl, 6-phenylaminocarbonylbenzothiazol-2-yl, 6-(3-methylbenzylaminocarbonylbenzothiazol-2-yl, 6-indan-1-ylaminocarbonyl-benzothiazol-2-yl, 6-(2-fluoro)benzylaminocarbonylbenzothiazol-2-yl, 6-(4-chloro)benzylcarbonylaminobenzothiazol-2-yl, 6-(3-chloro)benzylcarbonylaminobenzothiazol-2-yl, 6-cyclohexylcarbonylaminobenzothiazol-2-yl, 6-(4-isopropyl)phenylcarbonylaminobenzothiazol-2-yl, 6-naphth-1-ylcarbonylaminobenzothiazol-2-yl, 6-naphth-1-ylcarbonylaminobenzothiazol-2-yl, 6-benzylsulfonylaminobenzothiazol-2-yl, and 6-pyrid-4-ylaminocarbonylbenzothiazol-2-yl.

Compounds of formula I in which R^1 represents a group of formula $NHX^1(CH_2)_bR^3$ and R^2 represents a group of formula COR^4 have been found to show selectivity for tryptase over other serine proteases and are therefore preferred.

Accordingly, preferred compounds of formula I are those of general formulae

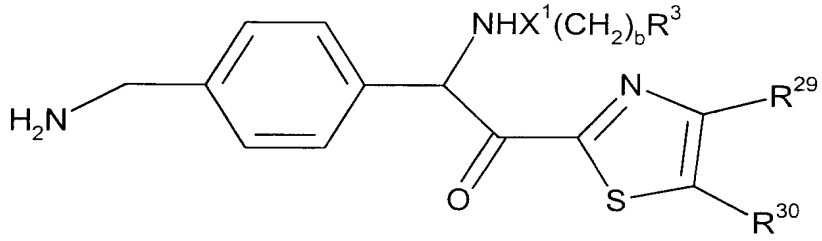


Id



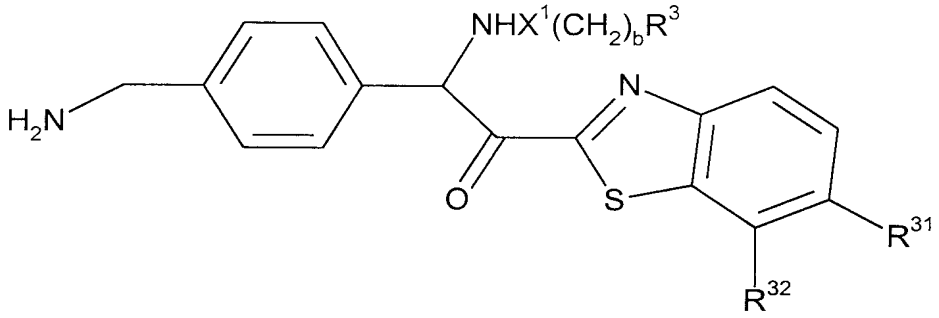
Ie

A particularly preferred group of compounds of formula Id is that of formula If



If

A particularly preferred group of compounds of formula Ie is that of formula Ig



Ig

Preferably R^{29} represents a hydrogen atom and R^{30} is a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected from a halogen atom; a cyano group; a nitro group; an (1-4C)alkyl group; a (2-4C)alkenyl group; a (2-4C)alkynyl group; a halo(1-4C)alkyl group; and a group of formula $(CH_2)_sX^{12}(CH_2)_tR^{35}$ in which s represents 0, 1 or 2, t represents 0, 1 or 2, X^{12} represents O, S, SO, SO_2, NR^{36}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{35} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{36} represents a hydrogen atom, a (1-4C)alkyl group or, together

with R^{35} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

An example of a particular value for R^{29} is a hydrogen atom.

Examples of particular values for R^{30} are phenyl, 2-naphthyl and 3,4-ethylenedioxphenyl.

Preferably R^{32} represents a hydrogen atom and R^{31} is a hydrogen atom; a halogen atom; a cyano group; a nitro group; an (1-4C)alkyl group; a (2-4C)alkenyl group; a (2-4C)alkynyl group; a halo(1-4C)alkyl group; a group of formula $(CH_2)_uX^{13}(CH_2)_vR^{37}$ in which u represents 0, 1 or 2, v represents 0, 1 or 2, X^{13} represents O, S, SO, SO_2, NR^{38}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{37} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group, an indanyl group, a pyridyl group, a naphthyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{38} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{37} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

Examples of particular values are:

for X^{13}: NHCO, CONH or SO_2NH;

for R^{37}: cyclohexyl, indan-2-yl, pyrid-4-yl, naphth-1-yl, naphth-2-yl, phenyl, 2-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methylphenyl, 4-methylphenyl, 4-isopropylphenyl and thien-2-yl;

for u: 0; and

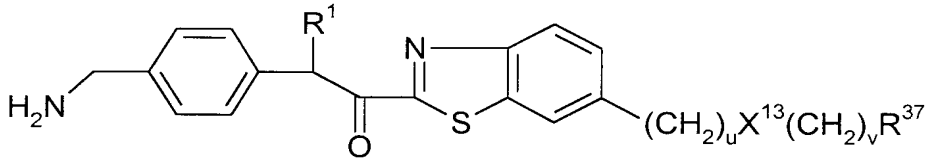
for v: 0 or 1.

Examples of particular values for R^{31} are hydrogen, benzylaminocarbonyl, phenylcarboxamido, 2-

thienylmethylaminocarbonyl, phenylaminocarbonyl, cyclohexylaminocarbonyl, cyclohexylamido, cyclohexylmethylaminocarbonyl, indan-2-ylaminocarbonyl, pyrid-4-ylaminocarbonyl, naphth-1-ylamido, naphth-2-ylamido, 3-methylbenzylaminocarbonyl, 4-methylbenzylaminocarbonyl, 2-fluorobenzyl-aminocarbonyl, 3-chlorobenzylamido, 4-chlorobenzylamido, benzylamido, benzylsulfonylamino and 4-isopropylbenzamido.

An example of a particular value for R^{32} is a hydrogen atom.

A particular sub-group of compounds of especial interest is that of formula



(Ih)

in which R^1 represents a hydrogen atom or a group of formula $NHX^1(CH_2)_bR^3$.

Compounds of formula Ih in which R^1 represents a hydrogen atom have been found to be highly potent as tryptase inhibitors. Those skilled in the art will appreciate that the compounds of formula Ih in which R^1 represents a hydrogen atom lack a chiral centre at the carbon atom bearing R^1, and that this is highly desirable in a molecule intended for development as a pharmaceutical.

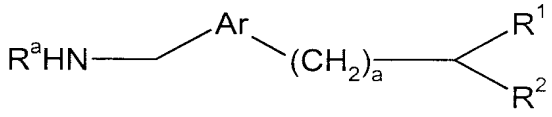
In the compounds of formula Ih, R^1 preferably represents a hydrogen atom or a group of formula $NHX^1(CH_2)_bR^3$ in which R^3 represents a (1-10C)alkyl, (3-10C)cycloalkyl, phenyl or naphthyl group.

Examples of preferred values for R^1 in formula Ih are hydrogen, acetamido, cyclohexylmethylamido and benzamido.

The term pharmaceutically acceptable salt refers to an acid addition or base salt of a compound of formula I. Examples of acid addition salts include salts formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid or sulfuric acid, and organic acids, such as acetic acid, trifluoroacetic acid, benzoic acid, oxalic acid, succinic acid, p-toluene sulfonic acid and methanesulfonic acid. Base salts include ammonium, sodium and potassium salts.

The term pharmaceutically acceptable metabolically labile amide refers to an amide formed between a pharmaceutically acceptable carboxylic acid and the amino group in the aminomethyl group of a compound of formula I, which amide is hydrolysed *in vivo* to afford the aminomethyl compound of formula I and the carboxylic acid. Examples of pharmaceutically acceptable carboxylic acids include acetic acid.

According to another aspect, the present invention provides a process for the preparation of a compound of formula I, or a pharmaceutically acceptable metabolically labile ester thereof or a pharmaceutically acceptable salt of said compound of formula I or said pharmaceutically acceptable metabolically labile amide thereof, which comprises deprotecting a compound of formula



II

in which R^a represents a protecting group, followed if desired by

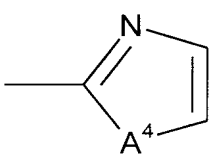
(ii) forming a pharmaceutically acceptable metabolically labile amide; or

(ii) forming a pharmaceutically acceptable salt.

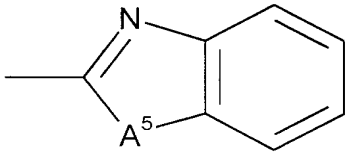
The protection and deprotection of amine groups is well known, and is described, for example, in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY., 1973 and Greene and Wutts, Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, NY., 1991. Examples of amine protecting groups are acyl groups, for example t-butoxycarbonyl.

An acyl protecting group, such as t-butoxycarbonyl is conveniently removed by reaction with an acid, for example an inorganic acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid. The reaction is conveniently performed at a temperature of from -10 to 100°C. Convenient solvents include halogenated hydrocarbons, such as dichloromethane.

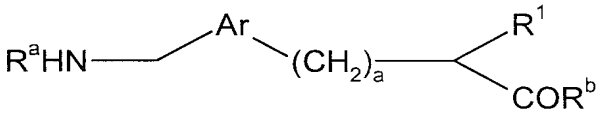
Compounds of formula II in which R^2 represents COR^3 and R^3 represents an unsubstituted or substituted heteroaromatic group of formula



or

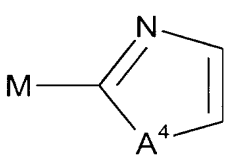


may be prepared by reacting a compound of formula



III

in which R^b represents an alkoxy group, such as methoxy, or N-(1-4C)alkoxy-N-(1-4C)alkylamino, such as N-methoxy-N-methylamino with an unsubstituted or substituted compound of formula



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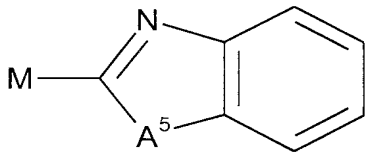
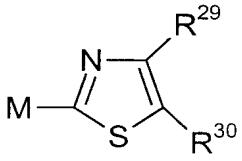
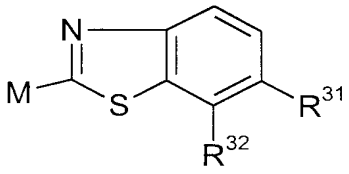


IV V

in which M represents a metal residue, such as a lithium, magnesium, copper or zinc residue. The reaction is conveniently performed at a temperature of -78 to -25°C. Convenient solvents include ethers, such as tetrahydrofuran. The compound of formula IV or V may be generated in situ from the corresponding compound of formula IV or V in which M represents a hydrogen atom by reaction with an appropriate organometallic reagent, for example an alkyl lithium such as n-butyl lithium.

It will be appreciated that an unsubstituted or substituted compound of formula IV or V includes compounds of formula





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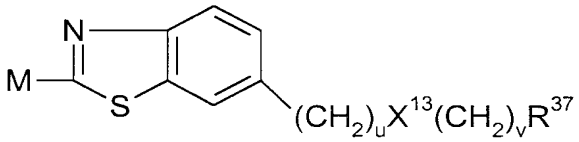
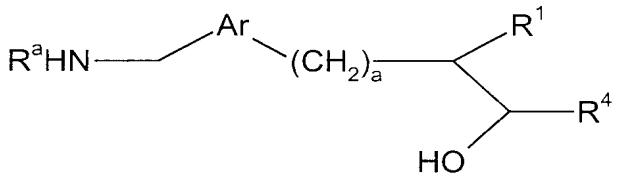




VI

The oxidation is conveniently effected using Dess-Martin reagent, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one. Other oxidizing agents include pyridinium chlorochromate, pyridinium dichromate, potassium permanganate and dimethylsulfoxide/oxalyl chloride.

Compounds of formula III in which R^b represents N-(1-4C)alkoxy-N-(1-4C)alkylamino may be prepared by reacting a corresponding compound of formula III in which R^b represents alkoxy with an N-(1-4C)alkoxy-N-(1-4C)alkylamine, or a salt thereof such as a hydrochloride in the presence of an organometallic reagent, such as dimethylaluminium chloride.

Alternatively, they may be prepared by reacting a compound of formula III in which R^b represents a hydroxyl group with an N-(1-4)alkoxy-N-(1-4C)alkylamine, or a salt thereof, with a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in the presence of a base, such as triethylamine. A convenient solvent is dichloromethane.

Compounds of formula III in which R^1 represents a group of formula $NHX^1(CH_2)_bR^3$ and R^b represents alkoxy may be prepared by reacting a compound of formula III in which R^1 represents an amino group with a compound of formula

$$Z^1X^1(CH_2)_bR^3$$

VII

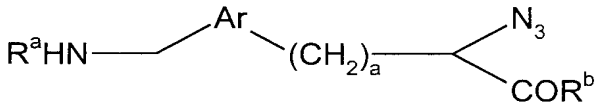
in which Z^1 represents a leaving atom or group.

The leaving atom or group represented by Z^1 may be, for example, a halogen atom, such as a chlorine atom. Alternatively, it may be generated *in situ*, for example by

reacting a compound of formula VII in which Z^1 represents hydroxyl with a coupling agent, for example a carbodiimide, such as 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide. The reaction is conveniently performed in the presence of a base, such as triethylamine, diisopropylethylamine, pyridine or 4-dimethylaminopyridine. Convenient solvents include amides, such as dimethylformamide and halogenated hydrocarbons, such as dichloromethane and chloroform. The reaction is conveniently performed at a temperature in the range of from 0 to 150°C.

Compounds of formula III in which R^1 represents an amino group and R^b represents alkoxy are known or may be prepared from known compounds by methods known in the art. See, for example, Tetrahedron (1977), 33(20), 2715-7 and European patent applications, publication numbers EP 31794 and EP 580008.

Compounds of formula III in which R^1 represents an amino group may also be prepared by reducing a compound of formula

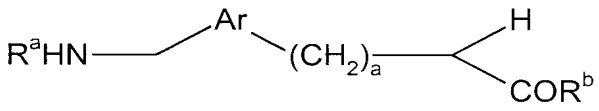


VIII

The reduction is conveniently performed by catalytic hydrogenation in the presence of a Group VIII metal catalyst, such as Raney nickel or palladium on charcoal. Convenient solvents include esters, such as ethyl acetate. The reduction is conveniently performed at a temperature in the range of from 0 to 100°C and a pressure of from 1 to 35 x 10^5 Pa.

Compounds of formula IV and V are generally known or may be prepared by methods known in the art. For example, 6-carboxybenzothiazole and 6-aminobenzothiazole may readily be converted into an amide derivative by reaction with an appropriate amine or carboxylic acid.

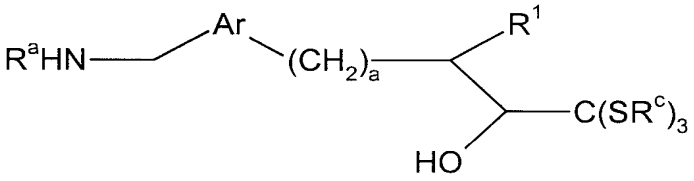
Compounds of formula VIII may be prepared by reacting a compound of formula



IX

with a strong base, such as potassium bis(trimethylsilyl)-amide, and a triorganosulfonylazide, such as triisopropyl-benzenesulfonyl azide, followed by an acid, such as acetic acid. The reactions are conveniently performed at a temperature of from -78 to 0°C. Suitable solvents include ethers, such as tetrahydrofuran.

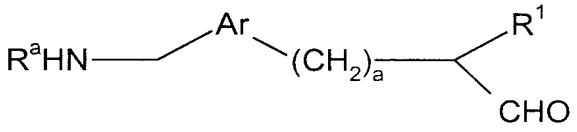
Compounds of formula VI may be prepared by reacting a compound of formula



X

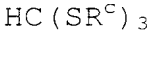
in which each R^c represents a (1-6C)alkyl group, such as ethyl, with a mercury (II) chloride, mercury oxide and an alcohol of formula HOR^4. The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. The alcohol of formula HOR^4 may also serve as reaction solvent.

Compounds of formula X may be prepared by reacting a compound of formula



XI

with a compound of formula



XII

in the presence of a strong base, such as t-butyllithium. The reaction is conveniently performed at a temperature in the range of from -78 to -25°C. Convenient solvents include ethers, such as tetrahydrofuran.

Compounds of formula XI may be prepared by reacting a compound of formula III in which R^b represents N-(1-4C)alkoxy-N-(1-4C)alkylamino with a reducing agent, such as diisobutylaluminium hydride. Convenient solvents include tetrahydrofuran.

Many of the intermediates described herein, including the compounds of formula II, III (where R^b represents N-methoxy-N-methylamine), VIII and XI are believed to be novel and are provided as further aspects of the invention.

The ability of compounds to inhibit tryptase may be determined by the method of Tapparelli et al., (1993) J. Biol. Chem., 268, 4734-4741.

The compounds exemplified herein have all been tested by this method and found to possess tryptase inhibitor activity with a Ki of less than 100μM. The tests were performed in 0.1 M phosphate buffer (to pH 7.4) containing 0.5 mg/ml heparin at ambient temperature using purified human lung tryptase (supplied by Dr. Andrew Walls, Immunopharmacology Group, Southampton General Hospital, Southampton, UK) and the chromogenic tryptase substrate S-2366 (supplied by Quadratech, Epsom, Surrey, UK). Compounds were dissolved in dimethylsulfoxide and tested at concentrations of from 1nM-100mM in 96 well microplates. Inhibitor activity was determined by measuring light absorption by p-nitroaniline (produced by the action of tryptase on the chromogenic substrate) at 405nm using a Dynatech MR 5000 reader (supplied by Dynex Ltd., Billinghurst, UK). SAS software was then used to determine Km (Michaelis constant) and Ki values. S-2366 was calculated to give a Km of 216μM.

The selectivity of compounds for tryptase over other serine proteases may be determined by the same test method, but using the appropriate chromogenic serine protease substrate.

As described hereinabove, it is envisaged that a variety of mast cell mediate diseases may be treated by the compounds of the present invention through their action as tryptase inhibitors.

According to another aspect, therefore, the present invention provides a method of inhibiting tryptase in a patient requiring such treatment, which comprises administering an effective amount of a compound of formula I, or a metabolically labile amide thereof, or a pharmaceutically acceptable salt of said compound of formula I or said metabolically labile ester thereof.

As used herein, the term treatment includes prophylaxis, amelioration or elimination of a condition for which a patient is being treated.

The term patient includes a warm blooded animal, such as a human, pig, horse, sheep, cow, mouse, hamster, guinea pig dog or chicken, and a reptile. Preferably, the patient is a human.

The effective amount, or dose of compound administered to a patient will of course be determined by the particular circumstances surrounding the case, including the species, size, age, weight and sex of the patient, the compound to be administered, the route of administration and the particular condition being treated. The compounds can be administered by a variety of routes, such as by oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes, or by inhalation. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about

0.1 mg/kg to about 25 mg/kg. The dose when administered by inhalation may be lower, for example in the range of from 0.01 to 2.0 mg for a patient weighing 70kg.

The present invention also provides the use of a compound of formula I, or a metabolically labile amide thereof, or a pharmaceutically acceptable salt of said compound of formula I or said metabolically labile ester thereof for the manufacture of a medicament for use as a tryptase inhibitor.

As described hereinabove, a tryptase inhibitors are envisaged to be useful in the treatment of a wide variety of conditions, including asthma, allergic rhinitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), Pulmonary fibrotic diseases, cirrhosis of the liver, Kimura's disease, pre-eclampsia, bleedling problems associated with menstruation and the menopause, Crohn's disease, colitis, multiple sclerosis, interstitial cystitis, wound healing, eczema, psoriasis, atopic dermatitis, urticaria, conjunctivitis, neurogenic inflammation, migraine headache, rheumatoid arthritis, atherosclerosis, cancer (particularly melanoma and tumour metastasis), pancreatitis and certain viral infections (Yong, Exp. Toxic Pathol, 1997, 49, 409; Steinhoff et al., Nat. Med., 2000, 6, 151; Downing and Miyan, Immunol. Today, 2000, 21, 281; Tetlow and Wooley, Ann. Rheum. Dis., 1995, 54, 549; Jeziorska, Salamonsen and Wooley, Biol. Reprod., 1995, 53, 312; Brain, Nat. Med., 2000, 6, 134, Olness et al., Headache, 1999, 39, 101.) The underlying principle is that a tryptase inhibitor should have utility where mast cells have been induced to degranulate by whatever mechanism, including anaphylactic reactions due to exogenous substances, e.g. morphine-induced bronchoconstriction (Bowman and Rand, 2nd edt., 1980.) The present invention accordingly provides the use of the compounds for the treatment of each of these conditions.

The compounds according to the invention may be administered with other pharmaceutically active agents, such as a bronchodilator, for example a β-agonist such as salbutamol or terbutaline; a methylxanthine, such as theophylline; a corticosteroid such as beclomethasone dipropionate; a chromolyn, such as sodium chromoglycate; a leukotriene antagonist such as zafirlukast or montelukast; a 5-lipoxygenase inhibitor, such as zileuton; or a tachykinin antagonist.

The compounds of the present invention are preferably administered to patients in a pharmaceutical composition.

According to another aspect, therefore, the present invention provides a pharmaceutical composition, which comprises a compound of formula I, or a pharmaceutically acceptable metabolically labile amide thereof, or a pharmaceutically acceptable salt of said compound of formula I or said pharmaceutically acceptable metabolically labile amide thereof, and a pharmaceutically-acceptable carrier.

The pharmaceutical compositions may be prepared by methods known in the art using well-known and readily available ingredients. Generally the active ingredient is mixed with the carrier, diluted by the carrier, or enclosed within the carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier acts as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Examples of carriers include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate,

alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The compositions can additionally contain lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

Formulation 3

Metered Dose Inhaler

	Quantity (g/inhaler)
Active Ingredient	0.02
Oleic acid	0.01
Dichlorodifluoromethane	10.50
Dichlorotetrafluorethane	4.50
Total	15.3

The following Examples illustrate the invention.

In the Examples, BOC refers to t-butoxycarbonyl, DMAP refers to 4-dimethylaminopyridine, DMF refers to dimethylformamide, TBTU refers to 2(1H-benzotriazol-1-yl)-1,3,3-tetramethyluronium tetrafluoroborate, THF refers to tetrahydrofuran, TFA refers to trifluoroacetic acid, DCM refers to dichloromethane and DIBAL-H refers to diisobutylene-aluminium hydride. The term Dess-Martin reagent refers to 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one.

Example 1

N-[α-(Benzothiazol-2-oyl)-N-(4-aminomethyl)benzyl] 4-isopropoxybenzamide trifluoroacetate salt

(i) Methyl 4-bromophenylacetate

To a solution of 4-bromophenylacetic acid (50g; 0.23mol) in methanol (250ml), was added thionyl chloride (18ml; 0.25mol) dropwise. The resulting mixture was stirred at room temperature for 1 hour and methanol was then removed *in vacuo*. Ethyl acetate (300ml) was added and the resulting solution was washed with water (3 x 150ml), 1M sodium bicarbonate solution (1 x 150ml) then dried ($MgSO_4$) and evaporated to give the ester (52.8g; 100%) as an orange oil.

^1H nmr ($CDCl_3$) 7.38 (2H, d, J=8.4Hz, Ar); 7.09 (2H, d, J=8.4Hz, Ar); 3.63 (3H, s, OMe); 3.51 (2H, s, 4-CH_2).

(ii) Methyl 4-cyanophenylacetate

To a solution of methyl 4-bromophenylacetate (20g; 0.088mol) in DMF (150ml) was added zinc cyanide (10.4g; 0.088mol) followed by tetrakis(triphenylphosphine)-palladium(0) (5g; 4.4mmol). The resulting mixture was stirred at 80°C for 5 hours, then allowed to cool to room temperature. Toluene (500ml) and 1M aqueous ammonia solution (500ml) were added and the organic layer washed with brine then dried ($MgSO_4$). Purification on silica gel afforded the cyano compound as a white solid (11.3g; 73%).

^1H nmr ($CDCl_3$) 7.65 (2H,d, J=8.4Hz, Ar); 7.42(2H, d, J=8.1Hz, Ar); 3.74 (3H, s, OMe); 3.72 (2H, s, CH_2).

(iii) 4-Cyanophenylacetic acid

To a solution of methyl 4-cyanophenylacetate (23.9g; 0.136mol) in ethanol (250ml) was added a solution of sodium hydroxide (6.0g; 0.15mol) in water (25ml). After 2 hours the ethanol was removed *in vacuo*. Ethyl acetate (300ml) and 5% aqueous HCl

solution (300ml) were added, the layers separated and the aqueous layer re-extracted with ethyl acetate (300ml). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to give the acid (21.6g; 99%).

^1H nmr ($CDCl_3$) 7.57 (2H, d, J=8.3Hz, Ar); 7.34 (2H, d, J=8.2Hz, Ar); 3.64 (2H, s, CH_2).

(iv) 4-(BOC-aminomethyl)phenylacetic acid

To a solution of 4-cyanophenylacetic acid (12.11g; 0.075mol) in water (163.5ml) and concentrated ammonia solution (33.9ml) was added Raney nickel (6.3g), and the resulting suspension was put under a hydrogen atmosphere. After 24 hours the reaction mixture was filtered through celite and evaporated *in vacuo* to give the amine (12.57g; 100%) as a pale blue solid.

To a solution of 4-(aminomethyl)phenylacetic acid (12.57g; 0.075mol) in water (50ml) and 1,4-dioxane (50ml) was added sodium hydroxide (3g; 0.075mol) and di-^{t}butyl dicarbonate (16.4g; 0.075mol) simultaneously. After 24 hours the 1,4-dioxane was removed *in vacuo* and the residual solution acidified with saturated citric acid solution (200ml). This was then washed with ethyl acetate (3 x 150ml), the combined organic layers dried ($MgSO_4$) and evaporated *in vacuo* to give the BOC-amine (17.6g; 88%) as a white solid.

^1H nmr ($CDCl_3$) 7.0 (4H, m, Ar); 4.65 (1H, bs, N-H); 4.09 (2H, d, 4-CH_2); 3.43 (2H, s, CH_2); 1.25 (9H, s, ^{t}Bu).

(v) Methyl 4-(BOC-aminomethyl)phenylacetate

To a solution of 4-(BOC-aminomethyl)phenylacetic acid (47.8g; 0.18mol) in methanol (200ml), was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (34.8g; 0.18mol) and DMAP (catalytic). After stirring for 18 hours the methanol was removed *in vacuo* and the reaction mixture partitioned between ethyl acetate (200ml) and saturated

citric acid solution (200ml). The organic phase was washed with sodium bicarbonate solution (200ml), brine (200ml), dried ($MgSO_4$) and evaporated to give the ester (49.8g; 99%).
^1H nmr ($CDCl_3$) 7.42 (4H, s, Ar); 5.02 (1H, bs, N-H); 4.48 (2H, d, J=5.7Hz, 4-CH_2); 3.87 (3H, s, OMe); 3.79 (2H, s, CH_2); 1.64 (9H, s, ^{t}Bu).

(vi) Methyl 4-(BOC-aminomethyl)-α-azidophenylacetate
To a solution of methyl 4-(BOC-aminomethyl)phenylacetate (9.34g; 0.033mol) in THF (100ml) at -78°C was added potassium bis(trimethylsilyl)amide (16.7g; 0.084mol) in THF (50 ml). After stirring for 30 minutes 2,4,6-triisopropylbenzenesulfonyl azide (31.1g; 0.101mol) was added as a solid. After 5 minutes, acetic acid (10ml; 0.175mol) was added and the reaction warmed to room temperature. The reaction mixture was then partitioned between ethyl acetate (500ml) and water (500ml) and the organic layer dried ($MgSO_4$). Purification on silica gel afforded the product (7.1g; 67%).
^1H nmr ($CDCl_3$) 7.28 (4H, s, Ar); 4.92 (1H, s, C-H); 4.25 (2H, s, 4-CH_2); 3.69 (3H, s, OMe); 1.38 (9H, s, ^{t}Bu).

(vii) Methyl 4-(BOC-aminomethyl)-α-aminophenylacetate
To a solution of methyl 4-(BOC-aminomethyl)-α-azidophenylacetate (7.1g; 0.022mol) in ethyl acetate (50ml) was added palladium on carbon (5%). The reaction vessel was taken up to 250psi (17.2×10^5 Pa) with hydrogen for 17 hours. The reaction mixture was filtered through cellite and evaporated *in vacuo* to give the amine (6.47g; 100%) as a pale solid.
^1H nmr ($CDCl_3$) 7.20 (2H, m, Ar); 7.12 (2H, m, Ar); 4.81 (1H, bs, N-H); 4.45 (1H, s, C-H); 4.18 (2H, d, 4-CH_2); 3.54 (3H, s, OMe); 2.09 (2H, bs, NH_2); 1.30 (9H, s, ^{t}Bu).

(viii) Methyl 4-(BOC-aminomethyl)-α-(4-isopropoxy)-benzoylaminophenylacetate

To a solution of 1-hydroxy-7-azabenzotriazole (153mg; 1.12mmol) in DMF (5ml) at 0°C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (215mg; 1.12mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes followed by addition of 4-isopropoxybenzoic acid (202mg; 1.12mmol). After stirring for a further 30 minutes methyl 4-(BOC-aminomethyl)-α-aminophenylacetate (300mg; 1.02mmol) was added and the reaction stirred for 18 hours. The DMF was removed *in vacuo* and the reaction mixture partitioned between ethyl acetate (40ml) and saturated citric acid solution (40ml). The organic layer was washed with 1M sodium bicarbonate solution (40ml) and dried ($MgSO_4$). Purification on silica gel afforded the amide (368mg; 81%) as a white solid.
^1H nmr ($CDCl_3$) 7.84 (2H, d, J=8.7Hz, Ar); 7.48 (2H, d, J=8.1Hz, Ar); 7.38 (1H, s, Ar); 7.11 (1H, d, J=6.1Hz, Ar); 6.97 (2H, d, J=8.8Hz, Ar); 5.82 (1H, d, J=6.8Hz, C-H); 4.69 (1H, septet, J=6.0Hz, $C\underline{H}(CH_3)_2$); 4.38 (2H, d, J=5.9Hz, 4-CH_2); 3.84 (3H, s, OMe); 1.53 (9H, s, ^{t}Bu); 1.43 (6H, d, J=6.0Hz, $CH(C\underline{H}_3)_2$).

(ix) 4-Isopropoxy-[α-(benzothiazol-2-oyl)-N-(4-BOC-aminomethyl)benzyl]benzamide

To a solution of benzothiazole (309µl; 2.82mmol) in THF (5ml) at -78°C was added ^{t}butyl lithium (1.66ml of 1.7m solution in pentane; 2.82mmol). After 15 minutes methyl 4-(BOC-aminomethyl)-α-(4-isopropoxy)benzoylaminophenylacetate (368mg; 0.807mmol) was added dropwise in THF (5ml) over 20 minutes. After stirring for 3 hours ammonium carbonate solution (2ml) was added dropwise and the reaction allowed to warm to room temperature. The reaction mixture was partitioned between ethyl acetate (50ml) and ammonium carbonate solution (50ml) and the

organic layer dried ($MgSO_4$). Purification on silica gel afforded the ketone (168mg; 37%).

^1H nmr ($CDCl_3$) 8.11 (1H, d, J=7.9Hz, Ar); 7.85 (1H, d, J=8.1Hz, Ar); 7.73 (2H, d, J=8.7Hz, Ar); 7.45 (4H, m, Ar); 7.14 (2H, d, J=8.0Hz, Ar); 7.03 (1H, d, J=6.9Hz, C-H); 6.81 (2H, d, J=8.7Hz, Ar); 4.53 (1H, septet, J=6.0Hz, $C\underline{H}(CH_3)_2$); 4.13 (2H, d, J=5.0Hz, 4-CH_2); 1.32 (9H, s, ^{t}Bu); 1.26 (6H, d, J=6.0Hz, $CH(C\underline{H}_3)_2$).

(x) 4-Isopropoxy-[α-(benzothiazol-2-oyl)-N-(4-aminomethyl)-benzyl]benzamide trifluoroacetate salt

To a solution of the 4-isopropoxy-[α-(benzothiazol-2-oyl)-N-(4-BOC-aminomethyl)benzyl]benzamide (168mg; 0.30mmol) in dichloromethane (10ml) was added trifluoroacetic acid (5ml). After 30 minutes the dichloromethane and trifluoroacetic acid were removed *in vacuo*. Purification by preparative HPLC gave the desired compound (110mg; 64%).

^1H nmr (d^4methanol) 8.22 (1H, m, Ar); 8.13 (1H, m, Ar); 7.88 (2H, d, J=8.9Hz, Ar); 7.71 (2H, d, J=8.2Hz, Ar); 7.65 (2H, m, Ar); 7.50 (2H, d, J=8.2Hz, Ar); 7.11 (1H, s, C-H); 7.01 (2H, d, J=8.8Hz, Ar); 4.7 (1H, q, J=6.0Hz, $C\underline{H}(CH_3)_2$); 4.11 (2H, s, 4-CH_2); 1.37 (6H, d, J=6.0Hz, $CH(C\underline{H}_3)_2$). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 13.29 min.

Examples 2-27

Using methods similar to that described in Example 1, and starting from carboxylic acids that were either commercially available or were prepared using literature procedures, the following compounds were prepared.

Example 2

Benzyl alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl-carbamate trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.22-8.19 (1H, m); 8.13-8.09 (1H, m); 7.70-7.58 (4H, m); 7.48-7.30 (7H, m); 6.79 (1H, s); 5.15 (2H, s); 4.09 (2H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 11.55 min.

Example 3

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-benzylamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.20-8.16 (1H, m); 8.12-8.09 (1H, m); 7.70-7.58 (4H, m); 7.47 (2H, d); 7.37-7.23 (5H, m); 6.93 (1H, t); 4.09 (2H, s); 3.69 (2H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 10.76 min.

Example 4

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-benzamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.15-8.11 (1H, m); 7.94-7.90 (2H, m); 7.78 (2H, d); 7.70-7.58 (3H, m); 7.55-7.49 (4H, m); 7.14 (1H, s); 4.11 (2H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 10.53 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.00 min, 402 $(M+1)^+$.

Example 5

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-cyclohexylacetamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.22-8.18 (1H, m); 8.13-8.09 (1H, m); 7.70-7.58 (4H, m); 7.48 (2H, d); 6.93 (1H, s); 4.10 (2H, s); 2.30-2.17 (2H, m); 1.86-1.67 (6H, m); 1.38-1.16 (3H, m); 1.10-0.95 (2H, m). Hplc (Magellan C8, Gradient 1,

Water/acetonitrile/trifluoroacetic acid) rt 11.05 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 0.33 min, 422 $(M+1)^+$.

Example 6

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-cyclohexylamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.22-8.18 (1H, m); 8.13-8.09 (1H, m); 7.70-7.58 (4H, m); 7.48 (2H, d); 6.90 (1H, s); 4.10 (2H, s); 2.50-2.39 (1H, m); 1.95-1.70 (5H, m); 1.56-1.23 (5H, m). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/ trifluoroacetic acid) rt 10.66 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 0.28 min, 408 $(M+1)^+$.

Example 7

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-4-isopropylbenzamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.15-8.11 (1H, m); 7.86 (2H, d); 7.78 (2H, d); 7.70-7.60 (2H, m); 7.50 (2H, d); 7.40 (2H, d); 7.13 (1H, s); 4.11 (2H, s); 3.06-2.97 (1H, m); 1.33 (3H, s); 1.30 (3H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 12.62 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/ trifluoroacetic acid) rt 0.33 min, 444 $(M+1)^+$.

Example 8

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-3,5-dimethylbenzamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.15-8.11 (1H, m); 7.78 (2H, d); 7.70-7.60 (2H, m); 7.54-7.46 (4H, m); 7.26 (1H, s); 7.12 (1H, s); 4.11 (2H, s); 2.40 (6H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 12.05

min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 0.40 min, 430 $(M+1)^+$.

Example 9

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-1-adamantanamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.22-8.19 (1H, m); 8.14-8.10 (1H, m); 7.69-7.60 (4H, m); 7.48 (2H, d); 6.82 (1H, s); 4.10 (2H, s); 2.12-2.04 (3H, m); 1.98-1.92 (6H, m); 1.90-1.75 (6H, m). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/ trifluoroacetic acid) rt 12.45 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.43 min, 460 $(M+1)^+$.

Example 10

N-[α-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-2-naphthamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.51 (1H, s, Ar); 8.23 (1H, m, Ar); 8.13 (1H, m, Ar); 8.00 (4H, m, Ar); 7.84 (1H, s, Ar); 7.81 (1H, s, Ar); 7.64 (4H, m, Ar); 7.54 (1H, s, Ar); 7.51 (1H, s, Ar); 7.20 (1H, s, C-H); 4.12 (2H, s, 4-CH_2). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 11.53 min.

Example 11

3-Methyl-4-nitro-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.16-8.12 (1H, m); 8.06 (1H, d); 7.97 (1H, s); 7.92-7.88 (1H, m); 7.79 (2H, d); 7.71-7.60 (2H, m); 7.52 (2H, d); 7.15 (1H, t); 4.12 (2H, s); 2.64 (3H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 17.03 min. LC/MS

(Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.18 min, 461 $(M+1)^+$.

Example 12

3,4-Dimethoxy-N-[alpha-(benzothiazol-2-oyl)-(4-aminomethyl)benzyl]benzamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.23-8.19 (1H, m); 8.14-8.10 (1H, m); 7.76 (2H, d); 7.70-7.56 (3H, m); 7.54-7.48 (3H, m); 7.11 (1H, s); 7.06 (1H, d); 4.11 (2H, s); 3.92 (3H, s); 3.90 (3H, s). Hplc (SymmetryShield Rp8, Gradient 3, Water/acetonitrile/trifluoroacetic acid) rt 3.87 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.82 min, 462 $(M+1)^+$.

Example 13

4-Dimethylamino-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide ditrifluoroacetate salt

^1H nmr (d_4 methanol) 8.23-8.19 (1H, m); 8.14-8.10 (1H, m); 7.82 (2H, d); 7.77 (2H, d); 7.69-7.59 (2H, m); 7.50 (2H, d); 7.10 (1H, s); 6.78 (2H, d); 4.11 (2H, s); 3.07 (6H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 9.70 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.10 min, 445 $(M+1)^+$.

Example 14

4-Acetylamino-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.15-8.11 (1H, m); 7.90 (2H, d); 7.82-7.60 (6H, m); 7.50 (2H, d); 7.12 (1H, s); 4.11 (2H, s); 2.19 (3H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 9.34 min. LC/MS

(Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.73 min, 459 $(M+1)^+$.

Example 15

2,3-Dihydro-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzofuran-5-amide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.24-8.20 (1H, m); 8.15-8.11 (1H, m); 7.82-7.72 (4H, m); 7.70-7.60 (2H, m); 7.50 (2H, d); 7.11 (1H, s); 6.83 (1H, d); 4.67 (2H, t); 4.11 (2H, s); 3.29 (2H, t). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 10.28 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.98 min, 444 $(M+1)^+$.

Example 16

4-Phenoxy-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^1H nmr (CD_3CN) 8.23 (1H, m, Ar); 8.12 (1H, m, Ar); 7.89 (3H, m, Ar); 7.68 (5H, m, Ar); 7.47 (3H, m, Ar); 7.25 (1H, m, C-H); 7.07 (4H, m, Ar); 4.12 (2H, s, 4-CH_2). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 13.16 min.

Example 17

4-Benzyloxy-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.21 (1H, m, Ar); 8.10 (1H, m, Ar); 7.88 (2H, d, *J*=8.9Hz, Ar); 7.76 (2H, d, *J*=8.3Hz, Ar); 7.64 (2H, m, Ar); 7.49-7.36 (7H, m, Ar); 7.10 (3H, m, C-H, Ar); 5.18 (2H, s, CH_2); 4.09 (2H, s, 4-CH_2). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 13.22 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.63 min, 508 $(M+1)^+$.

Example 18

4-(2-Phenoxyethoxy)-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.21 (1H, m, Ar); 8.10 (1H, m, Ar); 7.90 (2H, d, *J*=8.9Hz, Ar); 7.76 (2H, d, *J*=8.2Hz, Ar); 7.63 (2H, m, Ar); 7.48 (2H, d, *J*=8.2Hz, Ar); 7.30 (2H, m, Ar); 7.10-6.96 (6H, m, C-H, Ar); 4.41 (2H, m, CH_2); 4.36 (2H, m, CH_2); 4.09 (2H, s, CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.63 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.45 min, 538 $(M+1)^+$.

Example 19

4-Amino-3-methyl-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.20 (1H, d, *J*=6.9Hz, Ar); 8.11 (1H, m, Ar); 7.75 (2H, d, *J*=8.1Hz, Ar); 7.63 (4H, m, Ar); 7.48 (2H, d, *J*=8.1Hz, Ar); 7.07 (1H, s, C-H); 6.77 (1H, d, *J*=8.2Hz, Ar); 4.09 (2H, s, 4-CH_2); 2.21 (3H, s, Me). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.54 min.

Example 20

4-Methylsulfonyl-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.20 (1H, m, Ar); 8.12 (5H, m, Ar); 7.77 (2H, d, *J*=8.3Hz, Ar); 7.64 (2H, m, Ar); 7.50 (2H, d, *J*=8.3Hz, Ar); 7.14 (1H, s, C-H); 4.10 (2H, s, 4-CH_2); 3.18 (3H, s, Me). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.74 min, (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 10.45 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.89 min, 480 $(M+1)^+$.

Example 21

1-Acetyl-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]piperidin-4-amide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.50 (2H, d, *J*=8.4Hz, Ar); 8.05 (2H, m, Ar); 7.56 (4H, m, Ar); 4.52 (1H, m, C-H); 4.23 (2H, s, CH_2); 4.05 (1H, m, C-H); 3.38 (1H, m, C-H); 3.02 (1H, m, C-H); 2.26 (2H, m, 2C-H); 2.18 (3H, s, CH_3); 1.94 (2H, m, 2C-H); 1.26 (2H, m, 2C-H). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.44 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.45 min, 451 $(M+1)^+$.

Example 22

2-{1-[2(R)-(Acetylamino)propionyl]-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]}pyrrolidinamide trifluoroacetate salt

Prepared from Ac-L-Ala-L-Pro. ^{1}H nmr (d_4 methanol) 8.30 (4H, m, Ar); 7.71 (4H, m, Ar); 7.03 (1H, m, C-H); 4.72 (2H, m, 2C-H); 4.23 (2H, s, 4-CH_2); 3.76 (2H, m, CH_2); 2.19 (7H, m, CH_3, $2CH_2$); 1.50 (3H, m, CH_3).

Example 23

2-{1-[2(S)-(Acetylamino)propionyl]-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]}pyrrolidinamide trifluoroacetate salt

Prepared from Ac-D-Ala-L-Pro. ^{1}H nmr (d_4 methanol) 8.02 (2H, m, Ar); 7.52 (4H, m, Ar); 7.35 (2H, m, Ar); 6.75 (1H, m, C-H); 4.47 (2H, m, 2C-H); 3.97 (2H, s, 4-CH_2); 3.58 (2H, m, CH_2); 1.91 (7H, m, CH_3, $2CH_2$); 1.23 (3H, m, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.24 min. LC/MS (Magellan C18 Gradient 2,

water/acetonitrile/trifluoroacetic acid) rt 1.58 min, 508 $(M+1)^+$.

Example 24

2-{1-[2-(Thienylacetylamino)propionyl]-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]}-pyrrolidinamide trifluoroacetate salt

^1H nmr ($CDCl_3$) 8.13-6.66 (14H, m, C-H, 2N-H, Ar); 4.75-4.42 (2H, m, 2C-H); 3.90-3.33 (6H, m, $3CH_2$); 2.20-1.92 (6H, m, $2CH_2$, NH_2); 1.42-1.03 (3H, m, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.82 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.73 min, 590 $(M+1)^+$.

Example 25

2-{1-[2-(Cyclopentanoylamino)propionyl]-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]}-pyrrolidinamide trifluoroacetate salt

^1H nmr ($CDCl_3$) 8.20 (2H, bs, NH_2); 8.10 (2H, d, J=5.2Hz, Ar); 7.83 (2H, m, Ar); 7.43 (4H, m, Ar); 6.79 (1H, m); 6.68 (1H, d, J=5.6Hz, C-H); 4.63 (2H, m, 2C-H); 3.82-3.55 (4H, m, $2CH_2$); 2.60-1.05 (17H, m, Aliphatic, 2N-H). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.16 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.87 min, 562 $(M+1)^+$.

Example 26

2-{1-(Pyrrol-2-oyl)-N-[alpha-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]}pyrrolidinamide trifluoroacetate salt

^1H nmr (d_4 methanol) 8.12 (2H, m, Ar); 7.62 (4H, m, Ar); 7.45 (2H, m, Ar); 6.88 (3H, m, Ar); 6.25 (1H, s, C-H); 4.82 (1H, m, C-H); 4.07 (2H, s, CH_2); 3.91 (2H, m, CH_2); 2.05 (4H, m, $2CH_2$). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic

acid) rt 3.80 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.78 min, 488 $(M+1)^+$.

Example 27

N-[alpha-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-3-Benzyloxycarbonylamino-6-methyl-2-pyridone-1-acetamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.46 (2H, d, *J*=8.4Hz, Ar); 8.05 (3H, m, Ar); 7.54 (5H, m, Ar); 7.37 (5H, m, Ar); 6.38 (1H, d, *J*=8.3Hz, C-H); 5.64 (2H, s, CH_2); 5.21 (2H, s, CH_2); 4.19 (2H, s, CH_2); 2.57 (3H, s, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.44 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.25 min, 596 $(M+1)^+$.

Example 28

4-Methyl-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

(i) Methyl 4-(BOC-aminomethyl)-α-[(4-methyl)phenylsulfonyl-amino]phenylacetate

To a solution of methyl 4-(BOC-aminomethyl)-α-aminophenylacetate (300 mg; 1.02 mmol) in pyridine (10 ml) was added tosyl chloride (214 mg; 1.12 mmol), and the reaction mixture was stirred for 18 hours. The pyridine was removed *in vacuo* and the reaction mixture partitioned between ethyl acetate (40 ml) and saturated citric acid solution (40 ml). The organic layer was washed with 1M sodium bicarbonate solution (40 ml) and dried ($MgSO_4$). Purification on silica gel afforded the sulfonamide (410 mg; 90%) as a white solid.

^{1}H nmr (d_4 methanol) 7.54 (2H, d, *J*=8.1Hz, Ar); 7.16 (2H, d, *J*=8.1Hz, Ar); 7.07 (4H, s, Ar); 4.89 (1H, s, C-H); 4.06 (2H, s, 4-CH_2); 3.37 (3H, s, OMe); 2.28 (3H, s, CH_3); 1.33 (9H, s, ^{t}Bu).

(ii) 4-Methyl-[α-(benzothiazol-2-oyl)-N-(4-BOC-aminomethyl)benzyl]benzenesulfonamide

To a solution of benzothiazole (384 µl; 3.5 mmol) in tetrahydrofuran (5 ml) at -78°C was added ^{t}butyl lithium (2.07 ml of 1.7 m solution in pentane; 3.5 mmol). After 15 minutes methyl 4-(BOC-aminomethyl)-α-(4methyl)sulfonylaminophenylacetate (410 mg; 0.92 mmol) in tetrahydrofuran (5 ml) was added dropwise over 20 minutes. After stirring for 3 hours saturated ammonium chloride solution (2 ml) was added dropwise and the reaction allowed to warm to room temperature. The reaction mixture was partitioned between ethyl acetate (50 ml) and saturated ammonium chloride solution (50 ml) and the organic layer dried ($MgSO_4$). Purification on Biotage flash 40 afforded the ketone (110 mg; 22%).

(iii) 4-Methyl-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

To a solution of 4-methyl-[α-(benzothiazol-2-oyl)-N-(4-BOC-aminomethyl)benzyl]benzsulfonamide (110 mg; 0.2 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (5 ml). After 30 minutes the dichloromethane and trifluoroacetic acid were removed *in vacuo*. Purification by preparative hplc gave the desired compound (22 mg; 19%).

^{1}H nmr (d_4 methanol) 8.26-8.23 (1H, m); 8.12-8.08 (1H, m); 7.73-7.61 (4H, m); 7.57 (2H, d); 7.41 (2H, d); 7.15 (2H, d); 6.56 (1H, s); 4.07 (2H, s); 2.29 (3H, s). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 11.76 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.63 min, 452 $(M+1)^{+}$.

Examples 29 to 33

Using methods similar to that described in Example 28, and starting from sulphonyl chlorides that were either commercially available or were prepared using literature procedures, the following compounds were prepared.

Example 29

2,4,6-Trimethyl-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.19 (1H, d, *J*=7.8Hz, Ar); 8.08 (1H, m, Ar); 7.65 (2H, m, Ar); 7.57 (2H, d, *J*=8.2Hz, Ar); 7.41 (2H, d, *J*=8.3Hz, Ar); 6.71 (2H, s, Ar); 6.45 (1H, s, C-H); 4.07 (2H, s, 4-CH_2); 2.62 (6H, s, $2CH_3$); 2.03 (3H, s, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.22 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.46 min, 480 $(M+1)^+$.

Example 30

4-Isopropyl-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzensulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.02 (1H, m, Ar); 7.83 (1H, m, Ar); 7.45 (4H, m, Ar); 7.33 (2H, d, *J*=8.3Hz, Ar); 7.17 (2H, d, *J*=8.3Hz, Ar); 6.95 (2H, d, *J*=8.3Hz, Ar); 6.33 (1H, s, C-H); 3.82 (2H, s, 4-CH_2); 2.60 (1H, m, ^{i}PrC-H); 1.09 (6H, d, *J*=2.5Hz, $2CH_3$). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.24 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.27 min, 480 $(M+1)^+$.

Example 31

4-Phenyl-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl)benzyl]-benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.29(1H, m, Ar); 8.02 (1H, m, Ar); 7.87 (2H, m, Ar); 7.58 (6H, m, Ar); 7.43 (7H, m, Ar); 6.63 (1H, s, C-H); 4.02 (2H, s, 4-CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.48 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.36 min, 514 $(M+1)^+$.

Example 32

4-Acetylamino-N-[α-(benzothiazol-2-oyl)-4-(aminomethyl) benzyl]benzenesulfonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.19 (1H, d, *J*=7.9Hz, Ar); 8.03 (1H, d, *J*=9.1Hz, Ar); 7.63 (4H, m, Ar); 7.47 (4H, m, Ar); 7.32 (2H, d, *J*=8.9Hz, Ar); 6.52 (1H, s, C-H); 3.99 (2H, s, 4-CH_2); 2.08 (3H, s, CH_3). Hplc (MagellanC8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 10.86 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.79 min, 495 $(M+1)^+$.

Example 33

N-[α-(Benzothiazol-2-oyl)-4-(aminomethyl)benzyl]naphth-2-ylsulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.27-6.86 (15H, m, Ar); 6.07 (1H, s, C-H); 3.91 (2H, s, 4-CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.93min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.79 min, 488 $(M+1)^+$.

Example 34

Methyl α-oxo-β-benzoylamino-4-(aminomethyl)-benzenepropionate trifluoroacetate salt

(i) Methyl 4-(BOC-aminomethyl)-α-benzoylaminophenylacetate

To a solution of 1-hydroxy-7-azabenzotriazole (153 mg; 1.12 mmol) in dimethylformamide (5 ml) at 0°C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (215 mg; 1.12 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes followed by the addition of benzoic acid (137 mg; 1.12 mmol). After stirring for a further 30 minutes, methyl 4-(BOC-aminomethyl)-α-aminophenylacetate (300 mg; 1.02 mmol) was added and the reaction stirred for 18 hours. The dimethylformamide was removed *in vacuo* and reaction mixture partitioned between ethyl acetate (40 ml) and saturated citric acid solution (40 ml). The organic layer was washed with 1M sodium bicarbonate solution (40 ml) and dried ($MgSO_4$). Purification on silica gel afforded the amide (325 mg; 80%) as a white solid.

^{1}H nmr ($CDCl_3$) 7.84 (2H, m, Ar); 7.48 (5H, m, Ar); 7.31 (2H, m, Ar); 7.17 (1H, d, *J*=6.9Hz, N-H); 5.78 (1H, d, *J*=6.9Hz, C-H); 4.86 (1H, bs, N-H); 4.33 (2H, d, *J*=5.9Hz, 4-CH_2); 3.79 (3H, s, OMe); 1.47 (9H, s, ^{t}Bu).

(ii) α-[(N-methyl-N-methoxy)amido]-4-[BOC(aminomethyl)]-N-benzylbenzamide

To a solution of N,O-dimethylhydroxylamine hydrochloride (2.89 g; 0.03 mol) in anhydrous dichloromethane (200 ml) under argon at 0°C was added dimethylaluminium chloride (1M solution in hexane; 29.6 ml; 0.03 mol), dropwise from an addition funnel over 15 minutes. The reaction was stirred for 1 hour allowing the temperature to rise to room temperature. A solution of methyl 4-(BOC-aminomethyl)-α-benzoylaminophenylacetate (2.27 g; 5.7 mmol) in anhydrous dichloromethane (50 ml) was then added dropwise and the resulting mixture stirred for 2 hours. Tris buffer (pH8.2; 30 ml; 50 mmol) was added and the aqueous layer extracted with dichloromethane (2x15 ml). The combined

organic layers were dried ($MgSO_4$). Purification on silica gel afforded the product (2.13 g; 88%) as a white solid.
^1H nmr ($CDCl_3$) 7.73 (2H, m, Ar); 7.36 (5H, m, Ar); 7.20 (2H, m, Ar); 6.08 (1H, d, *J*=7.2Hz, C-H); 4.83 (1H, bs, N-H); 4.22 (2H, d, *J*=5.8Hz, 4-CH_2); 3.43 (3H, m, N-Me); 3.15 (3H, s, OMe); 1.37 (9H, s, ^tBu).

(iii) α-Carboxaldehydo-4-[BOC(aminomethyl)]-N-benzylbenzamide

To a solution of α-[(N-methyl-N-methoxy)amido]-4-[BOC(aminomethyl)]-N-benzylbenzamide (730 mg; 1.68 mmol) in anhydrous tetrahydrofuran (40 ml) under argon at -78°C was added DIBAL-H (1M solution in toluene; 5.05 ml; 5.05 mmol) dropwise by syringe. The reaction was stirred for 1.5 hours and then quenched with $Na_2SO_4.10H_2O$ (1 g; 3.1 mmol) at -78°C. The mixture was stirred vigorously and allowed to warm to room temperature then filtered and reduced *in vacuo* to afford the product (586 mg; 93%) as a viscous yellow oil.
^1H nmr ($CDCl_3$) 9.55 (1H, s, C(O)-H); 7.77 (2H, m, Ar); 7.40 (4H, m, Ar); 7.34 (3H, s, Ar); 5.65 (1H, d, *J*=5.8Hz, C-H); 4.91 (1H, bs, N-H); 4.22 (2H, d, *J*=6.0Hz, 4-CH_2);
1.37 (9H, s, ^tBu).

(iv) α-[1-Hydroxy-2-tris(ethylthiol)ethyl]-4-[BOC(aminomethyl)]-N-benzylbenzamide

To a solution of tris(ethylthio)methane (670 µl; 3.47 mmol) in anhydrous tetrahydrofuran (10 ml) under argon at -78°C was added ^nBuLi (2.5M in hexane; 1.04 ml; 2.60 mmol) dropwise by syringe. After stirring for 1 hour, α-carboxaldehydo-4-[BOC(aminomethyl)]-N-benzylbenzamide (160 mg; 0.43 mmol) in tetrahydrofuran (5 ml) was added dropwise over 5 minutes. The reaction was stirred for 2 hours at -78°C and then warmed to -

45°C for a further 2 hours before being quenched with saturated aqueous ammonium chloride solution (2 ml) and allowed to warm to room temperature. Diethyl ether (10 ml) was added and the organic layer washed with brine (10 ml) and dried ($MgSO_4$). Purification on silica gel afforded the product (68 mg; 38%) as a viscous yellow oil.

^1H nmr ($CDCl_3$) 7.81 (2H, m, Ar); 7.61 (1H, d, J=7.4Hz, Ar); 7.44-7.33 (5H, m, Ar); 7.17 (1H, s, Ar); 5.52 (1H, d, J=7.3Hz, C-H); 4.72 (1H, bs, N-H); 4.21 (2H, d, J=5.8Hz, 4-CH_2); 3.91 (1H, s, C-H); 2.74 (6H, m, 3CH_2); 1.38 (9H, s, ^{t}Bu); 1.13 (9H, t, J=7.5Hz, 3CH_3).

(v) Methyl α-hydroxy-β-benzoylamino-4-(BOC(aminomethyl))-benzenepropionate

To a solution of α-[1-hydroxy-2-tris(ethylthiol)ethyl]-4-[BOC(aminomethyl)]-N-benzylbenzamide (68 mg; 0.12 mmol) in methanol (2 ml) and water (200 µl) was added mercury(II)oxide (24 mg; 0.11 mmol) and mercury(II)chloride (85 mg; 0.31 mmol). The resulting mixture was stirred at room temperature for 4 hours then filtered through celite, the pad was washed with methanol (1 ml) and dichloromethane (2x2 ml). Water (5 ml) and dichloromethane (5 ml) were added to the filtrate and the layers separated. The aqueous layer was washed with dichloromethane (3x5 ml) and the combined organics washed with 70% aqueous ammonium acetate (10 ml) which was then re-extracted with dichloromethane (3x5 ml) and the combined organics washed with concentrated aqueous ammonium chloride solution (5 ml), dried ($MgSO_4$) and reduced *in vacuo* to afford the product (52 mg; 100%) as a gum.

^1H nmr ($CDCl_3$) 7.69 (2H, d, J=8.2Hz, Ar); 7.44-7.0 (7H, m, Ar); 5.64 (1H, d, J=8.9Hz, C-H); 4.82 (1H, bs, N-H); 4.53 (1H, s, C-H); 4.20 (2H, d, J=5.7Hz, 4-CH_2); 3.76 (3H, s, OMe); 1.38 (9H, s, ^{t}Bu).

(vi) Methyl α-oxo-β-benzoylamino-4-(BOC(aminomethyl))-benzenepropionate

To a solution of methyl-α-hydroxy-β-benzoylamino-4-(BOC(aminomethyl))-benzenepropionate (52 mg; 0.12 mmol) in dichloromethane (5 ml) was added Dess-Martin Reagent (67 mg; 0.16 mmol). The reaction was stirred for 45 minutes then diethyl ether (10 ml), 1M sodium bicarbonate solution (5 ml) and sodium thiosulfate (0.5 g) were added and the reaction stirred vigorously. The reaction was further diluted with diethyl ether (10 ml) and water (5 ml) and the organic layer washed with 1M sodium bicarbonate solution (5 ml), water (2x5 ml). dried ($MgSO_4$) and reduced *in vacuo* to afford the product (44 mg; 85%) as a pale yellow solid.

^1H nmr ($CDCl_3$) 7.73 (2H, m, Ar); 7.47-7.11 (7H, m, Ar); 6.38 (1H, d, *J*=6.3Hz, C-H); 4.86 (1H, bs, N-H); 4.22 (2H, d, *J*=5.7Hz, 4-CH_2); 3.74 (3H, s, OMe); 1.38 (9H, s, ^tBu).

(vii) Methyl α-oxo-β-benzoylamino-4-(aminomethyl)-benzenepropionate trifluoroacetate salt

To a solution of methyl-α-oxo-β-benzoylamino-4-(BOC(aminomethyl))benzenepropionate (23 mg; 0.054 mmol) in dichloromethane (1 ml) was added trifluoroacetic acid (1 ml). The reaction was stirred or 50 minutes and then reduced *in vacuo* and purified by preparative hplc to afford the product (5.4 mg; 23%).

^1H nmr (D_2O) 7.50 (2H, m, Ar); 7.41-7.23 (7H, m, Ar); 5.26 (1H, s, C-H); 3.97 (2H, s, 4-CH_2); 3.57 (3H, s, OMe). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 2.49 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.21 min, 310 $(M+1-NH_3)^+$.

Example 35

1-[2-(Cyclopentanoylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

(i) N-[4-BOC(aminomethyl)benzyl]-1-(2-aminopropionyl)-2-pyrrolidinamide was prepared using standard peptide coupling procedures from Mono-BOC-1,4-bis(aminomethyl)benzene which was prepared as described in the literature (*J.Med.Chem*, 1989, 32, 391-396).

(ii) To a solution of 1-hydroxy-7-azabenzotriazole (36 mg; 0.26 mmol) in dimethylformamide (5 ml) at 0°C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (50 mg; 0.26 mmol), the reaction mixture was allowed to warm to room temperature over 30 minutes followed by addition of cyclopentanecarboxylic acid (28.2 µl; 0.26 mmol). After stirring for a further 30 minutes N-[4-BOC(aminomethyl)benzyl]-1-(2-aminopropionyl)-2-pyrrolidinamide (87 mg; 0.22 mmol) was added and the reaction stirred for 18 hours. The dimethylformamide was removed *in vacuo* and reaction mixture partitioned between ethyl acetate (40 ml) and saturated citric acid solution (40 ml). The organic layer was washed with 1M sodium bicarbonate solution (40 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the product dissolved in anhydrous dichloromethane (10 ml) and trifluoroacetic acid (5 ml) was added. After 1 hour the solvent was removed *in vacuo* and the residue purified by preparative chromatography to give the product (72 mg; 64%) as a white solid.

^1H nmr (d_4 methanol) 7.31 (4H, s, Ar); 4.50 (1H, m, C-H); 4.35 (3H, m, CH_2, C-H); 4.00 (2H, s, CH_2); 3.74 (1H, m, C-H); 3.58 (1H, m, C-H); 2.60 (1H, m, C-H); 2.14-1.49 (12H, m, Aliphatic); 1.25 (3H, d, J=7.0Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 7.46 min. LC/MS

(Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.50 min, 401 $(M+1)^+$.

Examples 36 to 48

The following compounds were prepared following the method of Example 35.

Example 36

1-[2-(Cyclohexylacetylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.37 (4H, s, Ar); 5.48 (1H, s, C-H); 4.58 (1H, q, J=7.0Hz, C-H); 4.42 (2H, m, CH_2); 4.07 (2H, s, CH_2); 3.84 (1H, m, C-H); 3.65 (1H, m, C-H); 2.26-1.90 (6H, m, Aliphatic); 1.69 (6H, m, Aliphatic); 1.32 (3H, d, J=7.0Hz, CH_3); 1.27-0.94 (5H, m, Aliphatic). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 8.48 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.64 min, 429 $(M+1)^+$.

Example 37

1-[2-(Thienoylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.82 (1H, m, Ar); 7.69 (1H, m, Ar); 7.42 (4H, s, Ar); 7.16 (1H, m, Ar); 4.81 (1H, m, C-H); 4.47 (3H, m, CH_2, C-H); 4.10 (2H, s, CH_2); 3.92 (1H, m, C-H); 3.74 (1H, m, C-H); 2.28-1.95 (4H, m, $2CH_2$); 1.48 (3H, d, J=7.0Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 7.54 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.30 min, 415 $(M+1)^+$.

Example 38

1-[2-(Thenoylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.31 (4H, m, Ar); 7.18 (1H, m, Ar); 6.86 (2H, m, Ar); 4.50 (1H, q, J=7.1Hz, C-H); 4.34 (3H, m, CH_2, C-H); 4.00 (2H, s, CH_2); 3.67 (3H, m, CH_2, C-H); 3.54 (1H, m, C-H); 2.13 (1H, m, C-H); 1.86 (3H, m, CH_2, C-H); 1.27 (3H, d, J=7.0Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 7.65 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 0.58 min, 429 $(M+1)^+$.

Example 39

1-[2-(p-Hydroxyphenylacetylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.41 (4H, s, Ar); 7.11 (2H, d, J=8.5Hz, Ar); 6.74 (2H, d, J=8.5Hz, Ar); 4.61 (1H, m, C-H); 4.43 (3H, m, CH_2, C-H); 4.11 (2H, s, CH_2); 3.77-3.60 (2H, m, CH_2); 3.45 (2H, s, CH_2); 2.24-1.90 (4H, m, $2CH_2$); 1.36 (3H, d, J=7.0Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 7.10 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.06 min, 439 $(M+1)^+$.

Example 40

1-[2-(Benzenesulfonylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.00 (2H, m, Ar); 7.75 (3H, m, Ar); 7.53 (4H, m, Ar); 4.52 (2H, m, CH_2); 4.32 (1H, q, J=6.8Hz, C-H); 4.24 (2H, s, CH_2); 4.19 (1H, m, C-H); 3.72 (2H, m, CH_2); 2.22-1.97 (4H, m, $2CH_2$); 1.38 (3H, d, J=6.9Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 8.05 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.54 min, 445 $(M+1)^+$.

Example 41

1-[2-(Benzylsulfonylamino)propionyl]-N-(4-(aminomethyl)benzyl)-2-pyrrolidinamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.60 (9H, m, Ar); 4.62 (3H, m, CH_2, C-H); 4.56 (2H, s, CH_2); 4.31 (2H, s, CH_2); 4.11 (1H, m, C-H); 3.63 (2H, m, CH_2); 2.42 (1H, m, C-H); 2.17 (3H, m, CH_2, C-H); 1.46 (3H, d, J=6.9Hz, CH_3). Hplc (Magellan C8, Gradient 1, Water/acetonitrile/trifluoroacetic acid) rt 8.34 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.59 min, 459 $(M+1)^+$.

Example 42

N-[4-(Aminomethyl)benzyl]-3-Benzyloxycarbonylamino-6-methyl-2-pyridone-1-acetamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.95 (1H, d, J=6.8Hz, Ar); 7.37 (9H, m, Ar); 6.27 (1H, d, J=7.7Hz, Ar); 5.21 (2H, s, CH_2); 4.88 (2H, s, CH_2); 4.45 (2H, m, CH_2); 4.10 (2H, s, CH_2); 2.34 (3H, s, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.56 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.73 min, 435 $(M+1)^+$.

Example 43

N-[4-(Aminomethyl)benzyl]-3-acetylamino-6-methyl-2-pyridone-1-acetamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 8.34 (1H, d, J=7.7Hz, Ar); 7.57 (4H, m, Ar); 6.40 (1H, d, J=7.8Hz, Ar); 5.05 (2H, s, CH_2); 4.60 (2H, s, CH_2); 4.25 (2H, s, CH_2); 2.49 (3H, s, CH_3); 2.32 (3H, s, CH_3). Hplc (Luna7, Gradient , Water/acetonitrile/trifluoroacetic acid) rt 1.05 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 0.42 min, 343 $(M+1)^+$.

Example 44

N-[4-(Aminomethyl)benzyl]-3-Benzyloxycarbonylamino-6-cyclohexylmethyl-2-pyridone-1-acetamide trifluoroacetate salt

^{1}H nmr ($CDCl_3$) 7.88 (4H, m, 3N-H, Ar); 7.54 (1H, bs, N-H); 7.29 (5H, m, Ar); 7.02 (4H, s, Ar); 6.05 (1H, d, *J*=7.5Hz, Ar); 5.11 (2H, s, CH_2); 4.52 (2H, s, CH_2); 4.15 (2H, s, CH_2); 3.68 (2H, s, CH_2); 2.42 (2H, d, *J*=6.8Hz, CH_2); 1.63 (4H, m, $2CH_2$); 1.40 (1H, m, C-H); 1.14 (4H, m, $2CH_2$); 0.87 (2H, m, CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.37 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.43 min, 517 $(M+1)^+$.

Example 45

4-Methyl-N-[4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.86 (2H, d, *J*=8.3Hz, Ar); 7.48 (6H, m, Ar); 4.19 (2H, s, CH_2); 4.16 (2H, s, CH_2); 2.55 (3H, s, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.24 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.74 min, 291 $(M+1)^+$.

Example 46

2,4,6-Trimethyl-N-[4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.34 (4H, m, Ar); 7.02 (2H, s, Ar); 4.08 (4H, s, $2CH_2$); 2.61 (6H, s, $2CH_3$); 2.31 (3H, s, CH_3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.67 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.83 min, 319 $(M+1)^+$.

Example 47

4-Phenyl-N-[4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.95 (2H, d, *J*=8.5Hz, Ar); 7.76 (2H, d, *J*=8.6Hz, Ar); 7.65 (2H, d, *J*=8.0Hz, Ar); 7.49 (3H, m, Ar); 7.35 (4H, s, Ar); 4.14 (2H, s, CH_2); 4.02 (2H, s, CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 3.95 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.32 min, 353 $(M+1)^+$.

Example 48

4-Acetylamino-N-[4-(aminomethyl)benzyl]benzenesulphonamide trifluoroacetate salt

^{1}H nmr (d_4 methanol) 7.74 (4H, m, Ar); 7.35 (4H, s, Ar); 4.08 (2H, s, CH_2); 4.07 (2H, s, CH_2); 2.17 (3H, s, CH3). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 2.60 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 1.45 min, 334 $(M+1)^+$.

Example 49

N-[α-((6-Benzylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

(i) N-benzyl-benzothiazole-6-carboxamide

To a solution of benzothiazole-6-carboxylic acid (1.0 g; 5.6 mmol) in anhydrous dichloromethane (5 ml) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.17 g; 6.1 mmol) and benzylamine (0.66 g; 6.1 mmol). The resulting reaction mixture was stirred at room temperature for 18 hours. Water (5 ml) and ethyl acetate (10 ml) were added, the white

precipitate was filtered off and the filtrate layers were separated. The organic layer was washed with water (10 ml), brine (10 ml) and dried ($MgSO_4$). Evaporation afforded the product as a yellow solid which was combined with the white precipitate collected earlier and recrystallised from ethyl acetate and hexane to afford the product as pale yellow crystals (540 mg; 36%).

^1H nmr ($d_4$methanol) 9.25 (1H, s, Ar); 8.46 (1H, s, Ar); 8.01 (1H, d, J=8.7Hz, Ar); 7.90 (1H, d, J=8.6Hz, Ar); 7.19 (5H, m, Ar); 4.50 (2H, s, CH_2).

(ii) N-[α-(6-Benzylamidobenzothiazol-2-oyl)-4-(BOC-aminomethyl)benzyl]benzamide

To a solution of N-benzyl-benzothiazole-6-carboxamide (540 mg; 2.01 mmol) in anhydrous tetrahydrofuran (20 ml) at -78°C under argon was added ^{t}butyl lithium (3.35 ml of 1.7m solution in pentane; 5.7 mmol) dropwise. After 10 minutes a solution of methyl 4-(BOC-aminomethyl)-α-benzoylaminophenylacetate (229 mg; 0.57 mmol) in anhydrous tetrahydrofuran (5 ml) was added by cannula. The reaction was stirred for 45 minutes and then saturated aqueous ammonium chloride solution (5 ml) was added and the reaction allowed to warm to room temperature. Ethyl acetate (35 ml) and water (10 ml) were added and the layers separated, the organic layer was washed with saturated aqueous ammonium chloride solution (5 ml), water (5 ml) and brine (5 ml) and dried ($MgSO_4$). Purification on silica gel gave the crude product as a yellow solid (111 mg; 30%).

(iii) N-[α-((6-Benzylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

To a solution of N-[α-((6-Benzylamido)benzothiazol-2-oyl)-4-(BOC-aminomethyl)benzyl]benzamide (100 mg; 0.16 mmol) in anhydrous dichloromethane (5 ml) was added trifluoroacetic acid

(2 ml). After 1 hour the dichloromethane and trifluoroacetic acid were removed *in vacuo*. Dichloromethane (10 ml) and water (10 ml) were added and the layers separated, the organic layer was washed with 5% aqueous hydrochloric acid solution (2×10 ml) and the combined aqueous layers washed with dichloromethane (10 ml). The aqueous layers were purified by preparative hplc to give the desired compound (2 mg; 2%) as a white solid.
^{1}H nmr ($d_4$methanol) 8.48 (1H, d, *J*=1.4Hz, Ar); 8.14 (1H, d, *J*=8.7Hz, Ar); 7.99 (3H, m, Ar); 7.77 (2H, m, Ar); 7.65 (2H, d, *J*=7.9Hz, Ar); 7.47-7.16 (8H, m, Ar); 6.98 (1H, s, C-H); 4.51 (2H, s, CH_2); 3.98 (2H, s, CH_2).

Example 50
N-[alpha-(6-(Benzoylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

(i) 6-Aminobenzothiazole
To a solution of 6-nitrobenzothiazole (1 g; 5.6 mmol) in ethanol (10 ml) was added 5% palladium on charcoal (catalytic). The reaction was put under a hydrogen atmosphere and stirred for 20 hours. The suspension was filtered through celite and washed through with ethanol (2x10 ml). The filtrate was reduced *in vacuo* and purified on silica gel to afford the product (770 mg; 92%) as a yellow crystalline solid.
^{1}H nmr ($CDCl_3$) 8.62 (1H, s, Ar); 7.81 (1H, d, *J*=8.7Hz, Ar); 7.08 (1H, d, *J*=2.4Hz, Ar); 6.80 (1H, m, Ar); 3.80 (2H, bs, NH_2).

(ii) 6-(Benzoylamino)benzothiazole
To a solution of benzoic acid (860 mg; 6.67 mmol) in dichloromethane (20 ml) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.28 g; 6.67 mmol) and 6-aminobenzothiazole (1 g; 6.67 mmol). The reaction was stirred

for 20 hours then ethyl acetate (20 ml) and brine (20 ml) were added. The organic layer was washed with brine (20 ml), 1M sodium bicarbonate solution (20 ml), dried ($MgSO_4$) and reduced *in vacuo*. The crude product was purified by recrystallisation from ethyl acetate to give the product (770 mg; 45%) as white crystals.

^1H nmr ($d_4$methanol) 9.19 (1H, s, Ar); 8.64 (1H, d, *J*=2.0Hz, Ar); 8.02 (3H, m, Ar); 7.79 (1H, m, Ar); 7.57 (3H, m, Ar).

(iii) N-[α-(6-(Benzoylamino)benzothiazol-2-oyl)-4-(BOCaminomethyl)benzyl]benzamide

To a solution of 6-(Benzoylamino)benzothiazole (770 mg; 3.03 mmol) in dry tetrahydrofuran (20 ml) under argon at -78°C was added ^{t}butyl lithium (3.6 ml of 1.7m solution in pentane; 6.06 mmol) dropwise. After stirring for 30 minutes at -78°C methyl 4-(BOC-aminomethyl)-α-benzoylaminophenylacetate (327 mg; 0.82 mmol) in tetrahydrofuran (10 ml) was added dropwise over 20 minutes. After stirring for 2 hours at -78°C, saturated ammonium chloride solution (3 ml) was added dropwise and the reaction allowed to warm to room temperature. Ethyl acetate (30 ml) and saturated ammonium chloride solution (30 ml) were added and the organic layer washed with water (30 ml), brine (30 ml) and dried ($MgSO_4$). Purification on silica gel gave the crude product (108 mg; 21%).

^1H nmr ($d_4$methanol) 8.67-7.32 (17H, m, Ar); 5.51 (1H, s, C-H); 4.20 (2H, s, CH_2); 1.43 (9H, s, ^{t}Bu).

(iv) N-[alpha-(6-(Benzoylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

To a solution of N-[alpha-(6-(Benzoylamino)benzothiazol-2-oyl)-4-(BOCaminomethyl)benzyl]benzamide (108 mg; 0.17 mmol) in anhydrous dichloromethane (5 ml) was added trifluoroacetic acid (2 ml) and the reaction stirred for 1 hour then reduced *in*

vacuo. The crude product was purified on silica gel to afford the product (53 mg; 49%).

^{1}H nmr ($d_6$dmso) 9.02 (1H, d, *J*=1.9Hz, Ar); 8.42 (3H, m, Ar); 8.13 (5H, m, Ar); 7.85-7.64 (8H, m, Ar); 7.11 (1H, m, C-H); 4.20 (2H, d, *J*=4.9Hz, CH_2). Hplc (Luna7, Gradient 4, Water/acetonitrile/trifluoroacetic acid) rt 4.07 min. LC/MS (Magellan C18 Gradient 2, water/acetonitrile/trifluoroacetic acid) rt 2.18 min, 521 $(M+1)^+$.

Example 51

N-[4-(Aminomethyl)benzyl]-6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetamide trifluoroacetate salt

(i) β-(Benzyloxycarbonyl)amino-2-naphthalene propanoic acid

To a solution of D-naphthylalanine (500 mg; 2.33 mmol) in dioxan and water was added benzylchloroformate (437 mg; 2.56 mmol) and sodium hydroxide (2.56 ml; 1M aqueous solution). The reaction mixture was stirred overnight and then reduced *in vacuo*. Ethyl acetate (30 ml) and saturated aqueous citric acid solution (30 ml) were added, the organic layer was washed with brine (30 ml) then dried ($MgSO_4$) and evaporated to give the product (385 mg; 47%).

(ii) N-[(1-methoxycarbonyl-2-^{t}butoxycarbonyl)]ethyl-β-(Benzyloxycarbonyl)amino-2-naphthalene propanamide

To a solution of β-(Benzyloxycarbonyl)amino-2-naphthalene propanoic acid (385 mg; 1.10 mmol) in dimethylformamide (10 ml) was added diisopropylethylamine (300 mg; 2.32 mmol), HOBT (164 mg; 1.21 mmol), TBTU (390 mg; 1.21 mmol) and Asp(O^tBu)OMe (246 mg; 1.21 mmol). The reaction was stirred overnight and reduced *in vacuo*. Ethyl acetate (30 ml) and saturated aqueous citric acid solution (30 ml) were added, the organic layer was washed

1M sodium bicarbonate solution (30 ml) then dried ($MgSO_4$) and evaporated to give the product.

(iii) N-[(1-methoxycarbonyl-2-^{t}butoxycarbonyl)]ethyl-β-amino-2-naphthalene propanamide

To a solution of N-[(1-methoxycarbonyl-2-^{t}butoxycarbonyl)]ethyl-β-(Benzyloxycarbonyl)amino-2-naphthalene propanamide in methanol (10 ml) was added 5% palladium on charcoal in water (5 ml). The reaction was put under a hydrogen atmosphere and stirred for three days then filtered through celite, washed through with methanol (3×20 ml) and water (2×20 ml) and reduced *in vacuo* to afford the product.

(iv) ^{t}Butyl-6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetate

A solution of N-[(1-methoxycarbonyl-2-^{t}butoxycarbonyl)]ethyl-β-amino-2-naphthalene propanamide in methanol (20 ml) was heated at reflux overnight and then reduced *in vacuo* to afford the product.

(v) 6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetic acid

To a solution of ^{t}Butyl 6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetate in dichloromethane (5 ml) was added trifluoroacetic acid (1 ml) and the reaction stirred for 2 hours. The reaction mixture was evaporated to afford the product (100 mg; 29% over 4 steps).

(vi) N-[4-(Aminomethyl)benzyl]-6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetamide trifluoroacetate salt

To a solution of 6-(naphth-2-yl-methyl)-2,5-dioxo-3-piperazineacetic acid (50 mg; 0.16 mmol) in dimethylformamide (2 ml) was added TBTU (52 mg; 0.16 mmol), triethylamine (45 µl; 0.32 mmol) and p-xylenediamine (already attached to 2-

chlorotritylchloride resin (1.05 mmol/g) following literature procedures, 31 mg; 0.032 mmol). The reaction was stirred overnight and then the resin washed with dimethylformamide (3×10 ml), dichloromethane (3×10 ml), dimethylformamide (3×10 ml) and dichloromethane (3×10 ml). The resin was then taken up in trifluroacetic acid (10 ml), water (1 ml) and triethylsilane (50 µl) and left for 1 hour then filtered and evaporated. Purification by preparative hplc gave the product (17 mg; 12%). ^{1}H nmr ($d_4$methanol) 7.89-7.31 (11H, m, Ar); 4.67 (2H, m, 2C-H); 4.31 (2H, m, CH_2);
4.09 (2H, s, CH_2); 3.42-2.53 (4H, m, $2CH_2$).

Example 52

N-[4-(Aminomethyl)benzyl]-6-(3-chlorobenzyl)-2,5-dioxo-3-piperazineacetamide trifluoroacetate salt

The title compound was made using the route of Example 51. ^{1}H nmr ($d_4$methanol) 7.29 (8H, m, Ar); 4.91-4.23 (4H, m, CH_2, 2C-H); 4.11 (2H, d, J=1.9Hz, CH_2); 3.52-2.50 (4H, m, $2CH_2$).

Examples 53 to 73

General Experimental

Analytical HPLC's were performed on a Shimadzu LC6 gradient system equipped with an autosampler. Eluant A consisted of aqueous TFA (0.1 %) and eluant B consisted of 90 % acetonitrile and 10 % water, containing TFA (0.1 %). Gradient 1 elution began at 5 % B and increased to 100 % B over seven minutes. Gradient 2 elution began at 5 % B and increased to 100 % B over ten minutes. Gradient 3 elution began at 5 % B for one minute, increasing to 20 % B after the fourth minute, 40 % B after the 14th minute and then 100 % B after the 15th minute. Gradient 5 elution began at 5 % B and increased to 100 % B over 15 mins. The columns used were Luna 2 C18 (3 µ, 30 mm x 4.6 mm), Luna 2

C18 (5 μ, 150 mm x 2 mm) , a Symmetry Rp8 (3.5 μ, 50 x 2.1 mm) and a Jupiter C18 (2 mm x 150mm).

LC/MS were performed on a PESCIEX single quadrupole API-150EX instrument, equipped with a Luna 2 C18 column (3 μ, 30 mm x 4.6 mm) eluting with 20 % to 100 % acetonitrile in water over five minutes (Gradient 4).

The following examples were prepared as described for **Example 49.**

Example 53

***N*-[α-((6-(4-Tolyl)methylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.70 ppm (1 H, s, benzothiazole C(7)H); 8.38 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 8.21 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 8.03 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.89 (2 H, d, *J* = 10 Hz, Ar); 7.70 (1 H, d, *J* = 8 Hz, Ph); 7.63 (4 H, t, *J* = 8 Hz, Ph); 7.40 (2 H, d, *J* = 9 Hz, Tolyl C(2)H/C(6)H or C(3)H/C(5)H); 7.30 (2 H, d, *J* = 9 Hz, Tolyl C(2)H/C(6)H or C(3)H/C(5)H); 7.20 (1 H, s, ArC<u>H</u>(N)C(O)); 4.70 (2 H, s, CH_2Tol); 4.22 (2 H, s, C<u>H_2</u>NH_2); 2.45 (3 H, s, CH_3).

HPLC (Luna 2, Gradient 1): rt = 4.33 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.37 minutes, 549 $(MH)^+$.

Example 54

***N*-[α-(6-(Cyclohexylmethylamido)benzothiazol-2-oyl-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.43 ppm (1 H, s, benzothiazole C(7)H); 8.12 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 7.92 (1H, d, *J* =

9 Hz, benzothiazole C(4)H or C(5)H); 7.77 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.63 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.50 - 7.35 (5 H, m, Ar); 6.97 (1 H, s, ArC<u>H</u>(N)C(O)); 3.97 (2 H, s, C<u>H</u>$_2$NH$_2$); 1.76 - 1.48 (6 H, m, cHex); 1.26 - 1.05 (3 H, m, cHex); 1.01 - 0.82 (2 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 4.43 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.42 minutes, 542 $(MH)^+$.

Example 55

***N*-[α-(6-(Phenylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.58 ppm (1 H, s, benzothiazole C(7)H); 8.30 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 8.17 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 7.85 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.76 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.57 (3 H, m, Ph); 7.40 (2 H, t, *J* = 7 Hz, Ph); 7.30 (2 H, m, Ph); 7.20 (1 H, t, *J* = 7 Hz, Ph); 5.83 (1 H, s, ArC<u>H</u>(N)C(O)); 4.04 (2 H, s, C<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.27 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.26 minutes, 521 $(MH)^+$.

Example 56

***N*-[α-((6-(3-Methylbenzyl)amido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.53 ppm (1 H, s, benzothiazole C(7)H); 8.20 (1 H, d, J = 9 Hz, benzothiazole C(4)H or C(5)H); 8.01 (1 H, d, J = 9 Hz, benzothiazole C(4)H or C(5)H); 7.82 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.68 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.55 - 7.41 (6 H, m, Ar); 7.15 (4 H, m, Ar); 7.02 (2 H, s, Ar); 4.52 (2 H, s, $C\underline{H}_2NH$); 4.03 (1 H, s, $C\underline{H}_2NH_2$); 2.28 (3 H, s, CH_3).

HPLC (Luna 2, Gradient 1): rt = 4.37 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.37 minutes, 550 $(MH)^+$.

Example 57

***N*-[α-[6-(*R*)-(Indan-1-amido)benzothiazol-2-oyl]-4-(aminomethyl)benzyl benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.48 ppm (1 H, s, benzothiazole C(7)H); 8.15 (1 H, d, J = 9 Hz, benzothiazole C(4)H or C(5)H); 7.97 (1 H, d, J = 9 Hz, benzothiazole C(4)H or C(5)H); 7.75 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.60 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.5 - 7.3 (4 H, m, Ar); 7.25 - 7.05 (4 H, m, Ar); 6.96 (1 H, s, Ar); 5.55 (1 H, m, Ar$C\underline{H}$(N)C(O)); 3.95 (1 H, s, $C\underline{H}_2NH_2$); 2.95 (1 H, m, indane C(1)H); 1.92 (2 H, m, indane C(3)H_2); 1.20 (2 H, m, indane C(2)H_2).

HPLC (Luna 2, Gradient 1): rt = 4.43 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.48 minutes, 562 $(MH)^+$.

Example 58

***N*-[α-(6-(2-Fluorobenzylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt.**

^{1}H NMR ($CDCl_3$): 8.48 ppm (1 H, s, Ar); 8.15 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 7.97 (1 H, d, *J* = 9 Hz, benzothiazole C(4)H or C(5)H); 7.78 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.68 (2 H, d, *J* = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.49 - 7.30 (5 H, m, Ar); 7.28 - 7.15 (2 H, m, Ar); 7.10 - 6.96 (3 H, m, 2 x Ar and ArC<u>H</u>(NBz)); 4.57 (2 H, s, C<u>H</u>$_2$NHC(O)); 3.98 (2 H, s, C<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 1): rt = 4.22 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.21 minutes, 554 $(MH)^+$.

Example 59

***N*-[α-(6-(Benzylamido)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]acetamide trifluoroacetate salt.**

^{1}H NMR (d_4 MeOH): 8.46 ppm (1 H, s, benzothiazole C(7)H); 8.13 (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.95 (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.52 (1 H, d, *J* = 7.5 Hz, Ar); 7.36 - 7.09 (8 H, m, Ar); 6.78 (1 H, s, C<u>H</u>NH); 4.51 (2 H, s, C<u>H</u>$_2$NHCO); 3.92 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.04 (3 H, s, NHCOC<u>H</u>$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.52 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.98 minutes, 473 $(MH)^+$.

Example 60

***N*-[α-(6-(Phenylamido)benzothiazol-2-oyl)-4(aminomethyl)benzyl] acetamide trifluoroacetate salt.**

^{1}H NMR (d_4 MeOH): 8.74 ppm (1 H, s, benzothiazole C(7)H); 8.37 (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 8.24 (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.82 (2 H, d, *J* =

7.25 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.72 (2 H, d, *J* = 7.25 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.56 - 7.21 (5 H, m, Ph); 6.98 (1 H, s, C<u>H</u>NH); 4.02 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.16 (3 H, s, NHCOC<u>H</u>$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.35 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.88 minutes, 459 $(MH)^+$.

The following ten examples were prepared in an analogous manner to **Example 50**, using the indicated carboxylic acid to form an amide from 6-aminobenzothiazole, and the indicated derivative of 4-(aminomethyl)phenylglycine.

Example 61

***N*-[α-(6-(Phenylacetylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

From phenylacetic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(benzoylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.54 ppm (1 H, s, benzothiazole C(7)H); 8.09 (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.96 - 7.82 (4 H, m, Ar); 7.79 - 7.21 (11 H, m, Ar); 4.08 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.76 (2 H, s, C<u>H</u>$_2$Ph).

HPLC (Luna 2, Gradient 1): rt = 4.37 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.26 minutes, 535 $(MH)^+$.

Example 62

***N*-[α-[(6-(4-Chlorophenyl)acetylamino)benzothiazol-2-oyl]-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

From 4-chlorophenylacetic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(benzoylamino)phenylacetate.

^{1}H NMR (d_4 methanol): 8.54 ppm (1 H, s, benzothiazole C(7)H); 8.09 (1 H, d, J = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.93 (2 H, d, J = 7 Hz, 4-chlorophenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.76 (2 H, d, J = 7 Hz, 4-chlorophenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.70 - 7.43 (6 H, m, Ar); 7.36 (4 H, s, Ar); 7.09 (1 H, s, C<u>H</u>NH); 4.10 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.76 (2 H, s, CH$_2$PhCl).

HPLC (Luna 2, Gradient 1): rt = 4.60 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.56 minutes, 570 $(MH)^+$.

Example 63

***N*-[α-[(6-(3-Chlorophenyl)acetylamino)benzothiazol-2-oyl]-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

From 3-chlorophenylacetic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(benzoylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.48 ppm (1 H, s, benzothiazole C(7)H); 8.00 (1 H, d, J = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.63 - 7.27 (10 H, m, Ar); 7.20 (4 H, s, Ar); 6.95 (1 H, s, C<u>H</u>NH); 3.94 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.64 (2 H, s, C<u>H</u>$_2$PhCl).

HPLC (Luna 2, Gradient 1): rt = 4.58 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.42 minutes, 570 $(MH)^+$.

Example 64

***N*-[α-[6-(Cyclohexanoylamino)benzothiazol-2-oyl]-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt.**

From cyclohexanecarboxylic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(benzoylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.39 ppm (1 H, s, benzothiazole C(7)H); 7.92 (1 H, d, J = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.79 (2 H, d, J = 7 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.61 (8 H, m, Ar); 6.92 (1 H, s, C<u>H</u>NH); 3.78 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.41 - 2.22 (1 H, m, C<u>H</u>CO cHex); 1.90 - 1.10 (10 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 4.52 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.34 minutes, 527 $(MH)^+$.

Example 65

***N*-[α-(6-(Phenylacetylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] acetamide trifluoroacetate salt.**

From phenylacetic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(acetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.40 ppm (1 H, s, benzothiazole C(7)H); 7.98 (1 H, d, J= 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.60 - 7.44 (3 H, m, Ar); 7.35 - 7.08 (7 H, m, Ar); 6.86 (1 H, s, C<u>H</u>NH); 3.86 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.61 (2 H, s, COC<u>H</u>$_2$Ph); 1.94 (3 H, s, NHCOC<u>H</u>$_3$).

HPLC (Luna 2, Gradient 1): rt = 3.68 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.91 minutes, 473 $(MH)^+$.

Example 66

***N*-[α-(6-(Benzoylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] cyclohexylacetamide trifluoroacetate salt.**

From benzoic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(cyclohexylacetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.52 ppm (1 H, s, benzothiazole C(7)H); 8.08 - 7.71 (5 H, m, Ar); 7.62 - 7.29 (6 H, m, Ar); 6.76 (1 H, s, Ar); 3.99 (2 H, s, $C\underline{H}_2NH_2$); 2.10 (2 H, s, $COC\underline{H}_2$cHex); 1.80 - 1.48 (5 H, m, cHex); 1.28 - 0.72 (5 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 4.48 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.42 minutes, 541 $(MH)^+$.

Example 67

***N*-[α-(6-(4-Isopropylbenzoylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] cyclohexylacetamide trifluoroacetate salt.**

From 4-isopropylbenzoic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(cyclohexylacetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.60 ppm (1H, s, benzothiazole C(7)H); 8.12 (1 H, d, J = 7.5 Hz, benzothiazole C(4)H or C(5)H); 8.05 - 7.80 (3 H, m, Ar); 7.68 (2 H, d, J = 7 Hz, Ar); 7.45 (4 H, d, J = 7.5 Hz, Ar); 6.90 (1 H, s, $C\underline{H}NH$); 4.10 (2 H, s, $C\underline{H}_2NH_2$); 3.08 - 2.96 (1 H, m, $CH(CH_3)_2$); 2.30 - 2.15 (2 H, m, $COCH_2$cHex); 1.87 - 1.60 (5 H, m, cHex); 1.43 - 1.18 (10 H, m, cHex, 2 x CH_3); 1.10 - 0.92 (2 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 5.18 minutes.

LC/MS (Luna 2, Gradient 4): rt = 3.10 minutes, 583 $(MH)^+$.

Example 68

***N*-[α-(6-(2-Naphthylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl]cyclohexylacetamide trifluoroacetate salt.**

From 2-naphthoic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(cyclohexylacetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.60 ppm (1 H, s, benzothiazole C(7)H); 8.42 (1 H, s, naphthyl C(1)H); 8.03 (1 H, d, J = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.98 - 7.74 (6 H, m, Ar); 7.60 - 7.45 (3 H, m, Ar); 7.35 (2 H, d, J = 7 Hz, Ar); 6.77 (1 H, s, C<u>H</u>NH); 3.94 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.18 - 2.02 (2 H, m, COC<u>H</u>$_2$cHex); 1.87 - 1.50 (6 H, m, cHex); 1.31 - 1.04 (3 H, m, cHex); 1.00 - 0.77 (2 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 5.06 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.88 minutes, 591 $(MH)^+$.

Example 69

***N*-[α-(6-(1-Naphthoylamino)benzothiazol-2-oyl)-4-(aminomethyl)benzyl] cyclohexylacetamide trifluoroacetate salt.**

From 1-naphthoic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(cyclohexylacetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 8.69 ppm (1 H, s, benzothiazole C(7)H); 8.38 - 7.40 (13 H, m, Ar); 6.88 (1 H, s, C<u>H</u>NH); 4.10 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.32 - 2.08 (2 H, m, COC<u>H</u>$_2$cHex); 1.92 - 1.58 (6 H, m, cHex); 1.39 - 0.89 (5 H, m, cHex).

HPLC (Luna 2, Gradient 1): rt = 4.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.66 minutes, 591 $(MH)^+$.

Example 70

***N*-[α-[(6-Benzylsulfonylamino)benzothiazol-2-oyl]-4-(aminomethyl)benzyl] acetamide trifluoroacetate salt.**

From benzylsulfonic acid and methyl 4-(t-butoxycarbonylamino-methyl)-α-(acetylamino)phenylacetate.

^{1}H NMR (d_4 MeOH): 7.80 ppm (1 H, d, *J* = 7.5 Hz, benzothiazole C(4)H or C(5)H); 7.56 (1 H, s, benzothiazole C(7)H); 7.41 (2 H, d, *J* = 7.2 Hz, Ar); 7.24 (2 H, d, *J* = 7.5 Hz, Ar); 7.13 - 6.80 (7 H, m, Ar); 6.64 (1 H, s, C<u>H</u>NH); 4.27 (2 H, s, C<u>H</u>$_2$NH$_2$); 3.82 (2 H, s, CH_2SO_2); 1.86 (3 H, s, $COCH_3$).

HPLC (Luna 2, Gradient 1): rt = 3.55 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 509 $(MH)^+$.

Example 71

***N*-Phenyl-2-[(4-aminomethyl)phenylacetyl]benzothiazol-6-amide trifluoroacetate salt.**

***N,O*-Dimethyl [4-(*N*-t-butoxycarbonylaminomethyl)phenylacetyl]hydroxylamide**

A solution of (*N*-t-butoxycarbonyl)-4-aminomethylphenylacetic acid (980 mg, 3.7 mmol) in dry dichloromethane (20 mL) was stirred at room temperature and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (740 mg, 3.9 mmol), *N,O*-dimethylhydroxylamine hydrochloride (380 mg, 3.9 mmol) and triethylamine (540 μL, 390 mg, 3.9 mmol) were added. The mixture was stirred for three days before it was diluted with dichloromethane (20 mL), washed with water (10 mL), 5 % aqueous HCl (10 mL), water (10 mL) and brine (10 mL) and dried over magnesium sulfate. After evaporation of the solvent under

reduced pressure the residue was purified by flash column chromatography on silica gel (2:1 hexane / acetone) to afford the amide (1.05 g, 92 %) as a pale yellow viscous oil.

_N_-Phenyl-benzothiazole-6-amide

Benzothiazole-6-carboxylic acid (1.0 g, 5.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2 g, 6.1 mmol) were stirred in dry dichloromethane (25 mL) and aniline (560 µL, 570 mg, 6.1 mmol) was added by syringe. The mixture was stirred overnight before water (10 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (25 mL). The combined organic solvents were washed with 5 % aqueous HCl (10 mL), water (10 mL) and brine (10 mL) and dried over magnesium sulfate. Evaporation of the solvents under reduced pressure afforded the amide (1.31 g, 92 %) as a pale orange solid which was not purified further.

_N_-phenyl-2-[(4-_N_-t-butoxycarbonylaminomethyl)phenylacetyl]benzothiazol-6-amide

A solution of _N_-phenyl benzothiazole-6-amide (214 mg, 0.84 mmol) in dry THF (5 mL) was cooled to -78 °C and n-butyllithium (2.07 M in hexane, 0.81 mL, 1.69 mmol) was added dropwise by syringe, causing the solution to turn red. After 15 minutes a solution of _N,O_-Dimethyl [4-(_N_-t-butoxycarbonylaminomethyl)phenyl-acetyl]hydroxylamide (130 mg, 0.42 mmol) in dry THF (1.5 mL) was added by cannula. The mixture was stirred for 1 hour before saturated aqueous NH_4Cl (4 mL) was added and the mixture allowed to warm to room temperature. The layers were separated and the organic phase diluted with diethyl ether (10 mL) before being washed with

water (5 mL) and brine (5 mL). The combined washings were extracted with ethyl acetate (5 mL) and the organics dried over magnesium sulfate. After evaporation of the solvents under reduced pressure, the residue was purified by flash column chromatography on silica gel (4:1 to 3:1 hexane / acetone and then methanol) to afford the benzothiazole ketone (81 mg, 38 %) as a pale yellow solid.

_N_-Phenyl-2-[(4-aminomethyl)phenylacetyl]benzothiazol-6-amide trifluoracetate salt

A solution of the N-protected benzothiazole ketone (75 mg) in dichloromethane (5 mL) was stirred at room temperature and trifluoroacetic acid (1 mL) was added. After 30 minutes the dichloromethane and excess trifluoroacetic acid were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 - 20 % methanol in chloroform) and then preparative HPLC to afford the free amine (14 mg, 23 %) as a pale yellow solid.

^{1}H NMR (d_6 DMSO): 8.92 ppm (1 H, s, benzothiazole C(7)H); 8.50 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 8.27 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 8.22 (1 H, br s, NH); 7.88 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.48 (5 H, s, Ph); 7.42 (2 H, d, J = 10 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 7.19 (1 H, t, J = 9 Hz, NH); 4.76 (2 H, s, $ArCH_2C(O)$); 4.10 (2 H, q, J = 6 Hz, $C\underline{H}_2NH_3^+$).

HPLC (Luna 2, File 8): rt = 12.06 min.

LC/MS (Luna 2, Gradient 4): rt = 2.53 min, 472 $(MH-NH_3)^+$.

Example 72

***N*-4-Pyridyl-2-[4-(aminomethyl)phenylacetyl]benzothiazol-6-amide bis(trifluoroacetate) salt.**

Prepared as in Example 71, using 4-aminopyridine instead of aniline.

^{1}H NMR (d_4 MeOH): 8.72 ppm (1 H, s, benzothiazole C(7)H); 8.59 (2 H, d, *J* = 9 Hz, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H); 8.48 (3 H, m, 4-aminomethylphenyl C(2)H/C(6)H or C(3)H/C(5)H and benzothiazole C(4)H or C(5)H); 8.13 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 7.37 (2 H, d, *J* = 9 Hz, 4-aminopirydyl C(2)H/C(6)H or C(3)H/C(5)H); 7.32 (2 H, d, *J* = 9 Hz, 4-aminopirydyl C(2)H/C(6)H or C(3)H/C(5)H); 4.58 (2 H, s, $ArCH_2C(O)$); 4.02 (2 H, s, $C\underline{H}_2NH_2$).

HPLC (Luna 2, Gradient 1): rt = 2.82 min.

LC/MS (Luna 2, Gradient 4): rt = 1.35 min, 403 $(MH)^+$.

Example 73

2-[4-(Aminomethyl)phenylacetyl] benzothiazole trifluoroacetate salt.

Prepared as in Example 71, using benzothiazole instead of 6-amidobenzothiazole

^{1}H NMR (d_4 MeOH): 8.12 (1 H, d, J = 8 Hz, benzothiazole C(7)H); 8.02 (1 H, d, J = 8 Hz, benzothiazole C(4)H); 7.52 (2 H, m, benzothiazole C(5)H, C(6)H); 7.45 (4 H, 2 x d, aminomethylphenyl); 4.55 (2 H, s, $ArC\underline{H}_2C(O)$); 4.01 (2 H, s, $C\underline{H}_2NH_3$).

HPLC (Jupiter C18, Gradient 5) rt = 10.2 mins

Example 74

4-(Aminomethyl)benzyl thiazol-2-yl ketone trifluoroacetate salt

synthesised as described for Example 71 using thiazole instead of 6-amidobenzothiazole

1H NMR (d4 MeOH) 8.00 ppm (1 H, d, J = 3Hz, thiazole C(5)H); 7.91 (1 H, d, J = 3Hz, thiazole C(4)H); 7.32 (4H, s, aminomethylphenyl); 4.41 (2 H, s, CH2CO); 3.98 (2 H, s, CH2NH2).

HPLC (Jupiter C18, Gradient 5): rt = 8.09 minutes)

Example 75

***N*-[α-[(5-Naphth-2-yl)thiazol-2-oyl]-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt**

i.) 2-Azido-2'-acetonaphthone

A solution of 2-bromo-2'-acetonaphthone (3.43 g, 13.8 mmol) in acetone (30 mL) was stirred at room temperature and sodium azide (1.79 g, 27.5 mmol) was added. The suspension was stirred for 18 hours, filtered and the solvent evaporated to afford the azido ketone (2.50 g, 86 %) which was not purified further.

ii.) 2-Amino-2'-acetonaphthone hydrochloride salt

A solution of the azide (2.0 g, 9.6 mmol) in methanol (50 mL) was stirred at room temperature and HCl (6 N, 2 mL, 12 mmol) and 10% Pd/C (0.25 g) were added. The flask was evacuated, the atmosphere replaced with hydgrogen and the suspension stirred vigorously for three hours. The catalyst was removed by filtration and the solvent evaporated to afford the amine hydrochloride as a pale yellow solid (2.10 g, 100 %).

iii.) *N*-Formyl-2-amino-2'-acetonaphthone

The amine hydrochloride (2.09 g, 9.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.0 g, 10.4 mmol) were stirred in dichloromethane (50 mL) and formic acid (715 μL, 870 mg, 18.9 mmol) and triethylamine (2.63 mL, 1.91 g, 18.9 mmol) were added by syringe. The mixture was stirred for 2.5 hours when further 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.2 mmol) and formic acid (500 μL,610 mg, 13.2 mmol) were added. The mixture was stirred for a further 15 hours. Water (30 mL) was then added and the layers were separated. The organic phase was washed with saturated aqueous citric acid (30 mL), water (30 mL), saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL) and dried over magnesium sulfate. Evaporation of the solvent afforded the formamide as a yellow-brown solid (1.85 g, 92 %) which was not purified further.

iv.) 5-(2-Naphthyl)thiazole

A solution of the formamide (1.85 g, 8.7 mmol) in dry THF (50 mL) was stirred at 0 °C under argon. Solid P_2S_5 (2.51 g, 11.3 mmol) was added and the mixture stirred for 75 minutes. Aqueous hydrochloric acid (2 N, 20 mL) was added and the mixture was diluted with diethyl ether (50 mL) and ethyl acetate (50 mL), causing a precipitate to form. This was removed by filtration through Celite before the aqueous phase was separated. The organic solution was washed with water (30 mL), saturated sodium bicarbonate (30 mL) and brine (30 mL) and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1 % diethyl ether in dichloromethane) to afford the thiazole as a yellow solid (840 mg, 46 %).

^{1}H NMR ($CDCl_3$) 8.75 ppm (1 H, s, thiazole C(2)H); 8.12 (1 H, s, thiazole C(4)H); 7.97 (1 H, s, naphthyl C(1)H); 7.85 - 7.74 (3 H, m, naphthyl C(4)H, C(5)H and C(8)H); 7.64 (1 H, d, J = 11 Hz, naphthyl C(3)H); 7.48 - 7.40 (2 H, m, naphthyl C(6)H and C(7)H).

_N_-[α-[(5-Naphth-2-yl)thiazol-2-oyl]-4-(aminomethyl)benzyl] benzamide trifluoroacetate salt

The remainder of the synthesis is analogous to Example 1 using methyl 4-(BOC-aminomethyl)-α-benzoylaminophenylacetate and 5-naphthyl-thiazole

^{1}H NMR (d_4 MeOH): 8.02 ppm (1 H, s, thiazole C(4)H); 8.21 (1 H, s, naphthyl C(1)H); 7.90 - 7.30 (13 H, m, Ar); 6.91 (1 H, s, ArC<u>H</u>(N)C(O)); 4.01 (2 H, s, ArC<u>H</u>$_2$NH$_2$).

HPLC (Luna 2, Gradient 2): rt = 4.75 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.75 minutes, 478 $(MH)^+$.

Example 76

_N_-[α-[5-(1,5-Benzodioxepin-7-yl)thiazol-2-oyl]-4-(aminomethyl)benzyl]benzamide

Prepared in an analogous fashion to Example 75, starting with 7-(2-bromoacetyl)-1,5-benzodioxepine.

^{1}H NMR (d_4 MeOH): 8.02 ppm (1 H, s, thiazole C(4)H); 7.86 - 7.70 (3 H, m, Ar); 7.53 - 7.20 (6 H, m, Ar); 7.14 - 7.03 (2 H, m, Ar); 6.90 - 6.80 (2 H, m, Ar and ArC<u>H</u>(N)C(O)); 4.17 - 4.03 (4 H, m, benzodioxepine C(2)H$_2$ and C(4)H$_2$); 3.73 (2 H, s, ArC<u>H</u>$_2$NH$_2$); 2.06 (2 H, pentet, J = 6 Hz, benzodioxepine C(3)H$_2$).

HPLC (Luna 2, Gradient 2): rt = 4.25 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.26 minutes, 500 $(MH)^+$.

Example 77

N-[alpha-(5-Phenylthiazol-2-oyl)-4-(aminomethyl)-benzyl]benzamide TFA.

Prepared in an analogous fashion to Example 75, starting with 2-bromoacetophenone

^{1}H NMR (d_4 methanol): 8.32 (1 H, s, CH thiazole); 7.78 - 7.60 (4 H, m, Ar); 7.57 - 7.44 (5 H, m, Ar); 7.40 (2 H, d, J = 7.2 Hz, Ar); 7.19 (2 H, d, J = 7.2 Hz, Ar); 6.39 (1 H, s, C<u>H</u>NHSO$_2$); 4.06 (2 H, s, C<u>H</u>$_2$NH$_2$); 2.29 (3 H, s, C<u>H</u>$_3$Tol).

Hplc (Luna 2, Gradient 1): rt = 4.61 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.03 minutes, 478 $(M + H)^+$.

Example 78

N-[alpha-(5-Phenylthiazol-2-oyl)-4-(aminomethyl)benzyl]-4-methylbenzenesulfonamide TFA.

Prepared in an analogous manner to Example 75 starting with 2-bromoacetophenone and using methyl 4-(BOC-aminomethyl)-α-[(4-methyl)phenylsulfonylamino]phenylacetate (see Example 27)

^{1}H NMR (d_6 dmso): 9.37 (1 H, d, J = 6.5 Hz, NH); 8.63 (1 H, s, CH thiazole); 8.20 (2 H, br s, NH$_2$); 7.97 (2 H, d, J = 7.2 Hz, Ar); 7.86 (2 H, d, J = 7.2 Hz, Ar); 7.70 - 7.47 (10 H, m, Ar); 6.89 (1 H, d, J = 6.5 Hz, C<u>H</u>NHCO); 4.07 (2 H, d, J = 4.9 Hz, C<u>H</u>$_2$NH$_2$).

Hplc (Luna 2, Gradient 1): rt = 4.24 minutes.

LC/MS (Luna 2, Gradient 4) : rt = 2.07 minutes, 428 $(M + H)^+$.

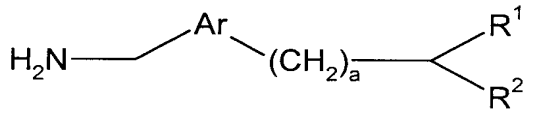
Example 79

N-[alpha-(Thiazol-2-oyl)-4-(aminomethyl)benzyl]benzamide trifluoroacetate salt

Prepared as described for Example 75 using thiazole as starting material and then using α-[(N-methyl-N-methoxy)amido]-4-(BOC-aminomethyl)-N-benzylbenzamide (see Example 33).

Claims

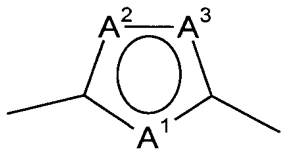
1. A compound of general formula I



I

in which:-

Ar represents an aromatic ring of formula



which is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group;

A^1 represents O, NH, S, CH or CH=CH; and A^2 and A^3 are each selected independently from CH, O, S, N and NH; provided that A^1, A^2 and A^3 are selected so that they, together with the carbon atoms to which they are attached, form an aromatic ring;

R^1 represents a hydrogen atom, an amino group or a group of formula $NHX^1(CH_2)_bR^3$;

R^2 represents a group of formula COR^4 or, when R^1 represents a group of formula $NHX^1(CH_2)_bR^3$, a hydrogen atom;

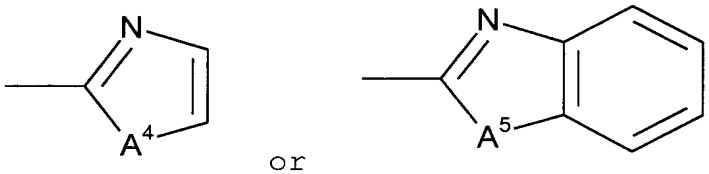
X^1 represents a bond, CO, SO_2, COO or CONH;

a represents 0, 1 or 2;

b represents 0 or an integer of from 1 to 4;

R^3 represents an unsubstituted or substituted aromatic, heterocyclic, (1-10C)alkyl, (2-10C)alkenyl, (2-10C)alkynyl or (3-10C)cycloalkyl group;

R^4 represents a group of formula COR^5, a group of formula CF_2R^6 or an unsubstituted or substituted heteroaromatic group of formula



or

R^5 represents a (1-6C)alkyl, fluoro(1-6C)alkyl or (3-10C)cycloalkyl group, an unsubstituted or substituted aromatic or heterocyclic group, a group of formula OR^7 or a group of formula NR^8R^9;

R^6 represents a fluorine atom, a (1-6C)alkyl, fluoro(1-6C)alkyl or (3-10C)cycloalkyl group, an unsubstituted or substituted aromatic or heterocyclic group, a group of formula $COOR^{10}$ or a group of formula $CONR^{11}R^{12}$;

A^4 represents O, NH or S;

A^5 represents O, NH or S; and

R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each selected independently from a hydrogen atom, a (1-6C)alkyl group, a (3-6C)cycloalkyl group and an unsubstituted or substituted aromatic group; or

(i) phenyl, naphthyl, furyl, benzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyridyl or pyrimidyl which is unsubstituted or substituted by (1-4C)alkylenenedioxy or by one, two or three substituents selected independently from a halogen atom;
a cyano group;
a nitro group;
an (1-4C)alkyl group;
a (2-4C)alkenyl group;
a (2-4C)alkynyl group;
a (3-7C)cycloalkyl(1-4C)alkyl group;
a halo(1-4C)alkyl group;
a group of formula $(CH_2)_cX^2(CH_2)_dX^3R^{13}$ in which c represents 0, 1 or 2, d represents 0, 1 or 2, X^2 represents O, S, SO, SO_2, NR^{14}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, X^3 represents a bond, O, S, SO, SO_2, NR^{15}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{13} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{14} and R^{15} each independently represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{13} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and
a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenenedioxy, or one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_eX^4(CH_2)_fR^{16}$ in which e represents 0, 1 or 2, f represents 0, 1 or 2, X^4 represents O, S, SO, SO_2, NR^{17}, CO, CONH, NHCO, OCONH, NHCOO,

COO, OCO, SO_2NH or $NHSO_2$, R^{16} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{17} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{16} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group;

(ii) pyrrolidinyl, piperidinyl, piperazinyl, or 2,3-dihydrobenzofuranyl unsubstituted or substituted by one, two or three of:

a (1-4C)alkyl group;

oxo;

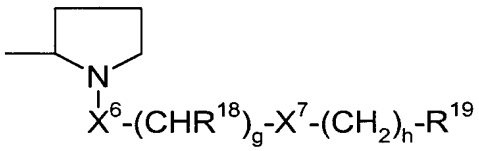
a group of formula $-X^6-(CHR^{18})_g-X^7-(CH_2)_h-R^{19}$ in which g represents 0, 1 or 2, h represents 0, 1 or 2, X^6 represents O, S, SO, SO_2, NR^{20}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, X^7 represents a bond, O, S, SO, SO_2, NR^{21}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{18} and R^{19} each independently represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group, a pyrrolyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group, a hydroxy group and a (1-4C)alkoxy group, and R^{20} and R^{21} each independently represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{19} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

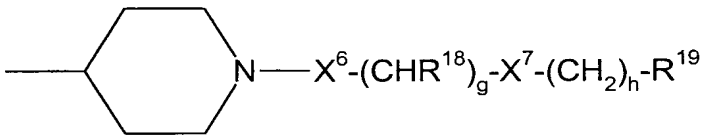
a group R^{22} in which R^{22} is (3-7C)cycloalkyl(1-4C)alkyl or a phenyl, naphthyl, phenyl(1-4C)alkyl or naphthyl(1-4C)alkyl group that is unsubstituted or substituted on any phenyl or

naphthyl moiety by (1-4C)alkylenedioxy or one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_iX^8(CH_2)_jR^{23}$ in which i represents 0, 1 or 2, j represents 0, 1 or 2, X^8 represents O, S, SO, SO_2, NR^{24}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{23} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{24} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{23} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; or

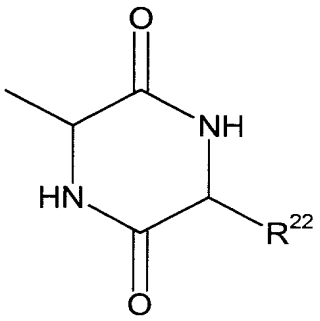
(iii) a (3-10C)cycloalkyl group that is unsubstituted or substituted by one, two or three (1-4C)alkyl groups.

8. A compound as claimed in claim 7, in which R^3 is a group of formula



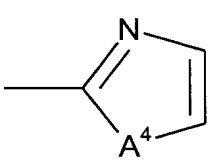


or

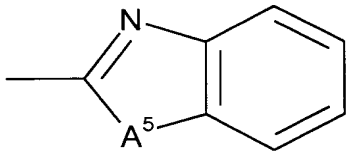


9. A compound as claimed in Claim 7, in which R^3 represents cyclohexyl, adamantyl, phenyl, 2-naphthyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-isopropylphenyl, 3-methyl-4-nitrophenyl, 3-methyl-4-aminophenyl, 4-isopropoxyphenyl, 3,4-dimethoxyphenyl, 4-phenylphenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, 4-(2-phenoxyethoxy)phenyl, 4-(N,N-dimethylamino)phenyl, 4-(N-acetylamino)phenyl, 4-methanesulphonylphenyl, 4-hydroxyphenyl, 2,3-dihydrobenzofuran-5-yl, 1-acetylpiperidin-4-yl, 1-(2-acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-(2-thienyl)-acetylaminopropionyl)pyrrolidin-2-yl, 1-(2-cyclopentanoylaminopropionyl)pyrrolidin-2-yl, 1-(pyrrol-2-oyl)pyrrolidin-2-yl, 3-benzyloxycarbonylamino-6-methyl-pyrid-2-one-1-yl, 1-(2-cyclohexylacetylaminopropionyl)-pyrrolidin-2-yl, 1-(2-(2-thienyl)carbonylaminopropionyl)-pyrrolidin-2-yl, 1-(2-(4-hydroxyphenyl)acetylaminopropionyl)-pyrrolidin-2-yl, 1-(2-phenylsulfonylaminopropionylpyrrolidin-2-yl, 1-(2-benzylsulfonylaminopropionylpyrrolidin-2-yl, 3-acetylamino-6-methyl-pyrid-2-one-1-yl, 3-benzyloxycarbonyl-amino-6-cyclohexylmethyl-pyrid-2-one-1-yl, 6-(naphth-2-yl)methyl-2,5-dioxopiperazin-3-yl or 6-(3-chlorobenzyl)-2,5-dioxopiperazin-3-yl.

10. A compound as claimed in any one of Claims 1 to 9, in which R^2 represents COR^4 and R^4 represents an unsubstituted or substituted heteroaromatic group of formula



or



in which the heteroaromatic group is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected independently from

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

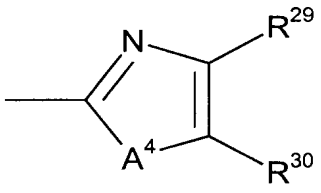
a halo(1-4C)alkyl group;

a group of formula $(CH_2)_kX^9(CH_2)_mR^{25}$ in which k represents 0, 1 or 2, m represents 0, 1 or 2, X^9 represents O, S, SO, SO_2, NR^{26}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{25} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula $(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents 0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$, or SO_2NH and R^{38} represent a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a(1-4C)alkyl group, R^{26} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{25} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

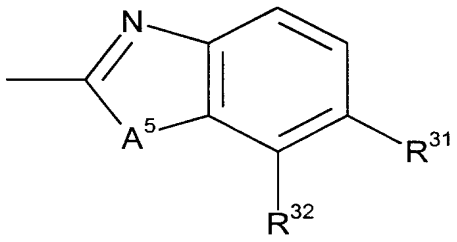
a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected

from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_nX^{10}(CH_2)_pR^{27}$ in which n represents 0, 1 or 2, p represents 0, 1 or 2, X^{10} represents O, S, SO, SO_2, NR^{28}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{27} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{28} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{27} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

11. A compound as claimed in Claim 10, in which the heteroaromatic group is a group of formula



or



in which:

R^{29} and R^{30} are together (1-4C)alkylenedioxy or are each selected independently from

a hydrogen atom;

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a halo(1-4C)alkyl group;

a group of formula $(CH_2)_qX^{11}(CH_2)_rR^{33}$ in which q represents 0, 1 or 2, r represents 0, 1 or 2, X^{11} represents O, S, SO, SO_2, NR^{34}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{33} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{34} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{33} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

a phenyl or naphthyl group that is unsubstituted or substituted by (1-4C)alkylenedioxy or by one or two substituents selected from a halogen atom, a cyano group, a nitro group, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a group of formula $(CH_2)_sX^{12}(CH_2)_tR^{35}$ in which s represents 0, 1 or 2, t represents 0, 1 or 2, X^{12} represents O, S, SO, SO_2, NR^{36}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{35} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group, R^{36} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{35} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group; and

R^{31} and R^{32} are together (1-4C)alkylenedioxy or are each selected independently from

a hydrogen atom;

a halogen atom;

a cyano group;

a nitro group;

an (1-4C)alkyl group;

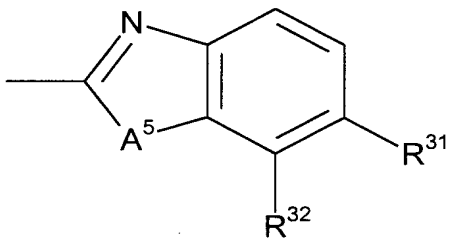
a (2-4C)alkenyl group;

a (2-4C)alkynyl group;

a halo(1-4C)alkyl group; and

a group of formula $(CH_2)_uX^{13}(CH_2)_vR^{37}$ in which u represents 0, 1 or 2, v represents 0, 1 or 2, X^{13} represents O, S, SO, SO_2, NR^{38}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{37} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula $(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents 0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$, or SO_2NH and R^{38} represent a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a(1-4C)alkyl group, R^{38} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{37} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

12. A compound as claimed in Claim 11, in which the heteroaromatic group is a group of formula

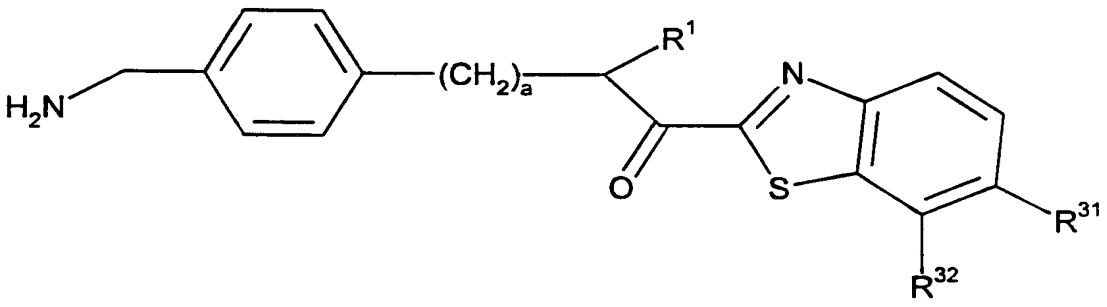


in which: R^{32} represents a hydrogen atom and R^{31} is a hydrogen atom; a halogen atom; a cyano group; a nitro group; an (1-

4C)alkyl group; a (2-4C)alkenyl group; a (2-4C)alkynyl group; a halo(1-4C)alkyl group; a group of formula $(CH_2)_uX^{13}(CH_2)_vR^{37}$ in which u represents 0, 1 or 2, v represents 0, 1 or 2, X^{13} represents O, S, SO, SO_2, NR^{38}, CO, CONH, NHCO, OCONH, NHCOO, COO, OCO, SO_2NH or $NHSO_2$, R^{37} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, an indanyl group, an aromatic or heteroaromatic group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a group of formula $(CH_2)_wX^{14}(CH_2)_xR^{38}$ in which w represents 0, 1 or 2, x represents 0, 1 or 2, X^{14} represents O, S, SO, SO_2, NH, CONH, NHCO, $NHSO_2$, or SO_2NH and R^{38} represent a hydrogen atom, a (1-4C)alkyl group or a phenyl group that is unsubstituted or substituted by a halogen atom, a (1-4C)alkyl group or a(1-4C)alkyl group, R^{38} represents a hydrogen atom, a (1-4C)alkyl group or, together with R^{37} and the nitrogen atom to which they are attached, a pyrrolidinyl, piperidinyl or morpholino group.

13. A compound as claimed in Claim 12, in which R^{37} represents a hydrogen atom, an (1-4C)alkyl group, a (2-4C)alkenyl group, a (2-4C)alkynyl group, a halo(1-4C)alkyl group, a (3-7C)cycloalkyl group, a thienyl group or a phenyl group that is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, an (1-4C)alkyl group and a (1-4C)alkoxy group.

14. A compound as claimed in any one of Claims 11 to 13, which is of the formula



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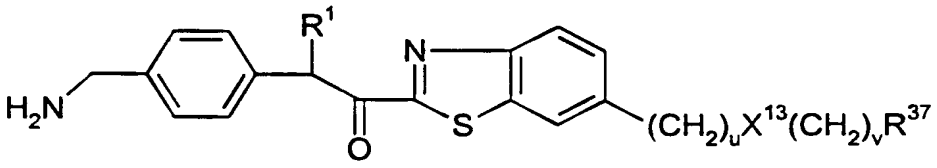
15. A compound as claimed in Claim 14, which is of the formula



(Ih)

in which R^1 represents a hydrogen atom or a group of formula $NHX^1(CH_2)_bR^3$.

16. A compound as claimed in any one of Claims 11 to 15, in which R^{31} is a group of formula $(CH_2)_uX^{13}(CH_2)_vR^{37}$ in which X^{13} is NHCO, CONH or SO_2NH, u is 0; and v is 0 or 1.

17. A compound as claimed in any one of Claims 11 to 16, in which R^1 represents a hydrogen atom or a group of formula $NHX^1(CH_2)_bR^3$ in which R^3 represents a (1-10C)alkyl, (3-10C)cycloalkyl, phenyl or naphthyl group.

18. A process for the preparation of a compound as claimed in any one of Claims 1-17, which comprises deprotecting a compound of formula

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 00/03832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/64 C07D417/12 C07D417/14 C07D213/75 C07D241/08
C07D277/24 C07D277/28 C07D417/04 C07C233/87 C07C311/18
C07C311/41 C07K5/062 A61K31/425 A61K31/18 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 84, no. 9, 1 March 1976 (1976-03-01) Columbus, Ohio, US; abstract no. 58646r, page 448; XP002156336 abstract & JP 50 083341 A (KYOWA HAKKO KOGYO CO., LTD.) 5 July 1975 (1975-07-05) --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2000	11/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 00/03832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/495 A61K38/05 A61P11/06 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! Chemical Abstract Services; AN 1975:40064, XP002156337 abstract and compound RN 54050-80-5 & CHEMICAL ABSTRACTS, vol. 82, no. 7, 17 February 1975 (1975-02-17) Columbus, Ohio, US; abstract no. 40064, MARKWARDT F ET AL: "Synthetic low molecular weight inhibitors of serum kallikrein" & BIOCHEM. PHARMACOL. , vol. 23, no. 16, 1974, pages 2247-2256, --- -/--	1-3,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 00/03832

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 24407 A (AMGEN INC.) 20 May 1999 (1999-05-20) the whole document, particularly page 32, 18th compound	1-21
X	WO 99 40083 A (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.) 12 August 1999 (1999-08-12) the whole document, particularly fig. 12	1-21
X	WO 96 09297 A (ARRIS PHARMACEUTICAL CORPORATION) 28 March 1996 (1996-03-28) the whole document	1-21
X	WO 95 32945 A (ARRIS PHARMACEUTICAL CORPORATION) 7 December 1995 (1995-12-07) cited in the application the whole document	1-21
X	WO 99 40073 A (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.) 12 August 1999 (1999-08-12) cited in the application the whole document	1-21
X	KIM B M ET AL: "Diphenylsilyldiethylene-(DPSide-) Group: A New Primary Amine Protection" TETRAHEDRON LETTERS, vol. 40, no. 29, 16 July 1999 (1999-07-16), pages 5333-5336, XP004170086 ISSN: 0040-4039 paqe 5335, table 2, compounds 6a-c	1
X	ANDRIEVSKY A ET AL: "Bipyrrole-based '2! catenane: a new type of anion receptor" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 120, no. 37, 23 September 1998 (1998-09-23), pages 9712-9713, XP002156335 the whole document	1

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13, 16-21 (all partly searched)

Present claims 1-13 and 16-21 relate to an extremely large number of possible compounds, their preparation and use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been directed to those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I wherein Ar is as recited in claim 2.

The initial phase of the search with regard to such compounds revealed however a very large number of documents relevant to the issue of novelty of the claims directed to compounds of formula I, wherein Ar is as recited in claim 2, R1 is NHX1(CH2)bR3 and R2 is hydrogen. So many documents disclosing such compounds were retrieved that it is impossible to determine which parts of the claims directed to such compounds may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

The search and the search report can therefore only be considered as complete for compounds of formula I wherein Ar is as recited in claim 2, and wherein R2 is COR4 as defined in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/GB 00/03832

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